THE OPTIMIZATION OF THE ALLYLATION OF PHENOLS *VIA* OXYPYRIDINIUM SALTS

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BY

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ABSTRACT

THESIS: The Optimization of the Allylation of Phenols *via* Oxypyridinium Salts

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Over the last few years, oxypyridinium salts have proven to be an efficient reagent in allowing the transfer of functional groups, especially 2-benzyloxy-1-methylpyridinium triflate (BnOPT). BnOPT allows for the transfer of benzyl groups to both alcohols and carboxylic acids to synthesize the corresponding benzyl ethers and benzyl esters, respectively. The reaction was investigated to determine whether the mechanistic pathway was more S_N1 or S_N2-favored. After investigating the successful transfer of *t*-butyl groups, possibly due to cation stabilization, it became logical to attempt to transfer other possible functional groups. If the reaction is mostly S_N1-favored, then allyl groups reactivity would be in between that of benzyl and *t*-butyl groups. Allyl groups were tested because of the vast usefulness in protecting group chemistry and in 3,3-rearrangements. 2-Allyloxy-1-methylpyridinium triflate (AMPT) allowed for the transfer of allyl protecting groups to carboxylic acids under relatively milder conditions effectively. Allyl transfers to phenols and alcohols were explored. This thesis accomplished the transfer of allyl groups to phenols to synthesize the corresponding allyl ethers efficiently *via* oxypyridinium salts under relatively mild conditions.

Table of Contents

List of Schemes

List of Figures

List of Tables

LIST OF ABBREVIATIONS

ADDP – 1,1-(Azodicarbonyl)dipiperidine

AMPT – 2-Allyloxy-1-methylpyridinium triflate

BnOPT – 2-Benzyloxy-1-methylpyridinium triflate

B(pin) – Bis(pinacolato)diboron

CMPI – 2-Chloro-1-methylpyridinium iodide, Mukaiyama's reagent

CSA – Camphorsulfonic acid

DCC – Dicyclohexylcarbodiimide

DCM – Dichloromethane

DMAP – 4-Dimethylaminopyridine

DMF – Dimethylformamide

HOTf – Triflic acid

MeOTf – Methyl triflate

$PhCF_3$ – Trifluorotoluene

CHAPTER I: BACKGROUND

1.1 Introduction to Protecting Groups

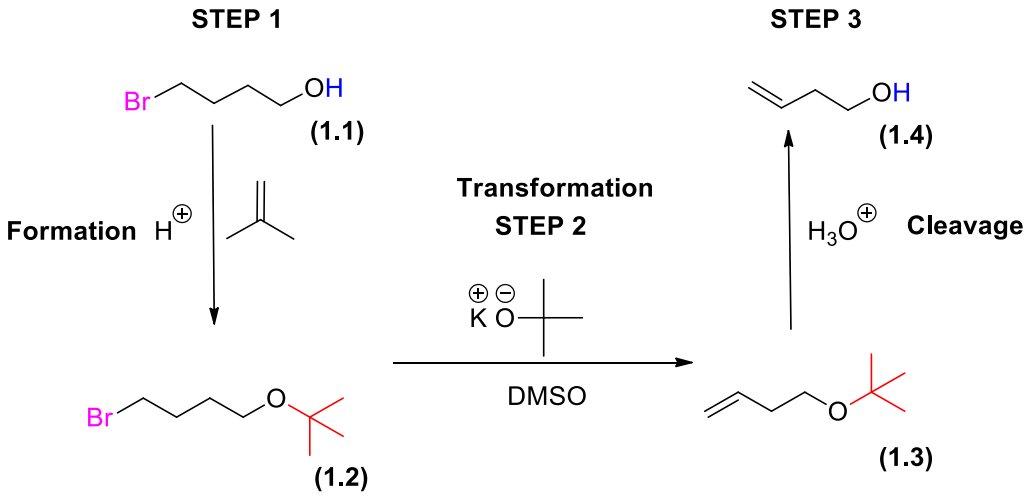
The selection and use of protecting groups is a significant consideration in synthetic chemistry. New reports of protective groups are a regular appearance. There are commonly five major functional groups that are coupled with protective groups. These include –OH, -NH_2, -SH, -COOH, and C=O. Protecting groups are molecules that react with a functional group to inhibit undesired reactions to achieve a desired product. When a functional group is protected, the reactivity of the protected group ensures that the reaction will not undergo undesired reactions.[1-6]

Protective groups fulfill certain requirements. A protective group must be able to react selectively to synthesize a protected product in a high yield. The protecting group must ensure that the product is stable enough to sustain harsher conditions. The protective group must also be selectively removed in a high yield. The protecting group should also be able to form a derivative that could be easily separated from byproducts. The protective group should restrain from too much reactivity from the surrounding reaction conditions .[1,2,4,5]

Protecting groups are particularly important for the protection of hydroxy groups. Alcohols persist in many biological and synthetic species, such as carbohydrates, nucleosides, steroids, polyethers, and some of the side chains of amino acids.[1,5,6] Protecting groups must be able to protect the alcohol functional group from oxidation, acylation, dehydration reactions, and other reactions.[1,3,5] Phenolic hydroxyl groups occur naturally in animal and plant life across the globe. Protection of the phenol is significant because they prevent the reaction from oxidizing agents. They also prevent nucleophilic attack in the presence of alkylating or acylating agents.[1,2,4,5]

There are three main steps for the protection of a molecule. The methods are commonly referred to as formation, transformation, and cleavage. Formation **(Scheme 1, Step 1)** occurs to

replace the proton of the functional group meant to be protected **(1.1)**, which causes the said functional group to become unreactive to surrounding reaction conditions with the additional of a *t*-butyl group **(1.2)**. Transformation **(Scheme 1, Step 2)** occurs when the compound **(1.2)** is now protected and allows the potassium *t*-butoxide to synthesize the corresponding product **(1.3)**.[1,5] During cleavage **(Scheme 1, Step 3)**, the protecting group on compound **1.3** was removed, and then the original reactive functionality was restored. The protecting group was then cleaved by treatment with aqueous acid to produce the final product of 3-Buten-1-ol **(1.4)**.[7] If the protecting group is not utilized, then the reaction could undergo undesired reactions. Pharmaceutical companies utilize these functional group strategies to synthesize desired products in a more efficient manner.[1,5]

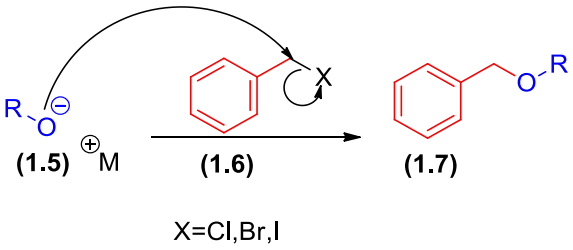


Scheme 1-1: Synthesis of 3-Buten-1-ol

1.2 Prominent Benzyl Etherification

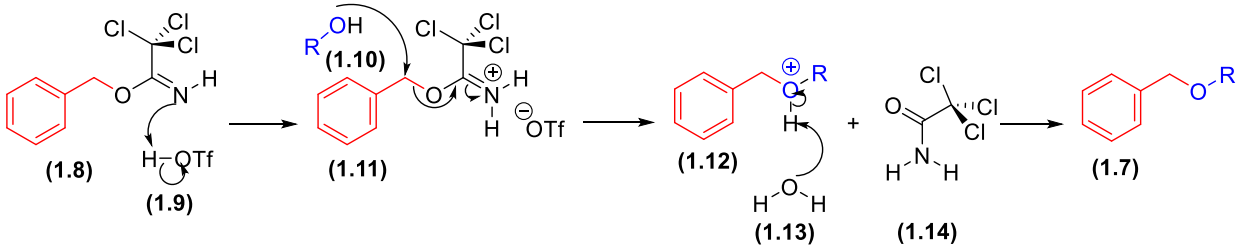
Benzyl groups are a very popular and widely used protecting group. The most common forms of synthesizing benzyl ethers are the Williamson-ether synthesis **(Scheme 1-2)** and the trichloroacetimidate-promoted etherification.[8,9] In Williamson-ether synthesis, the alkoxide salt **(1.5)** acts as a nucleophile to perform an S_N2 attack on the carbon adjacent to the halide **(1.6)**,

which allows for the synthesis of benzyl ethers **(1.7)** under basic conditions. The major limitation of the use of basic conditions is that the bases are able to react undesirably with other functional groups on the substrate.



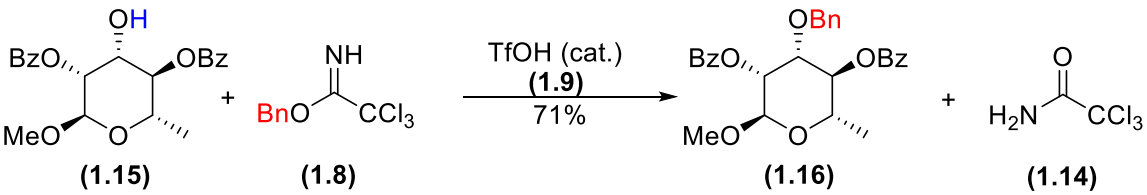
Scheme 1-2: Williamson Ether Synthesis

The trichloroacetimidate-promoted etherification method **(Scheme 1-3)** for producing ethers occurs under acidic conditions, requiring a strong acid such as triflic acid **(1.9)** for the reaction to be successful.[9] The nitrogen is activated *via* protonation. Once the nitrogen is protonated, the trichloroacetimidate amide **(1.14)** serves as an efficient leaving group. The alcohol **(1.10)** is then able to attack the benzylic carbon, generating the benzyl ether product **(1.7)**. However, this method requires a very strong acid to activate the leaving group.



Scheme 1-3: Mechanism of Benzyl Ether Formation *via* Trichloroacetimidate

There are many examples in literature showing the effectiveness of transferring benzyl groups using trichloroacetimidates **(Scheme 1-4)**.[9,10] The nitrogen on the trichloroacetimidate **(1.8)** is protonated by the strong acid **(1.9)** that activates said nitrogen, which allows for the ether product to be formed **(1.16)**. The main disadvantage to using trichloroacetimidate is the necessity of harsher acidic conditions.

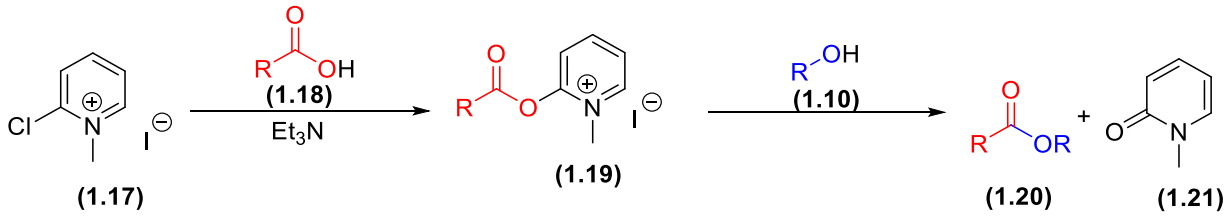


Scheme 1-4: Synthesis of Benzyl Ethers *via* Trichloroacetimidate

1.3 Mukaiyama's Reagent

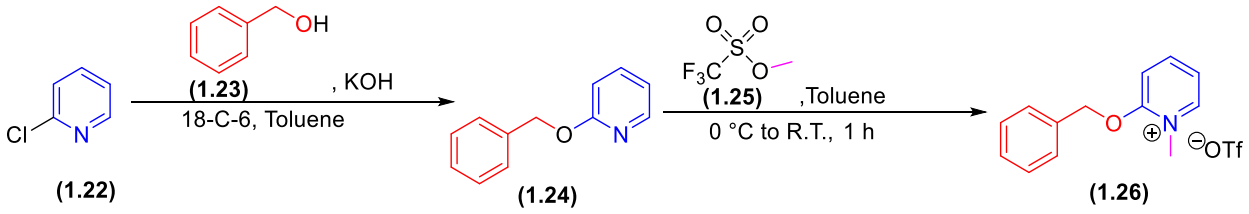
Benzyl transfer methods including Williamson-ether synthesis and the trichloroacetimidate-promoted etherification methods both had limitations regarding harsher conditions. Benzyl transfers *via* relatively mild conditions were then investigated. The popular reagent used to facilitate the synthesis of esters known as 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent, (CMPI)) **(1.17)** was then explored[11]. Mukaiyama's reagent is proven a very efficient coupling reagent for the synthesis of esters from carboxylic acids and primary and secondary alcohols **(Scheme 1-5)**.[11] The carboxylic acid **(1.18)** is able to act as a nucleophile in a nucleophilic aromatic substitution reaction with Mukaiyama's reagent **(1.17)** to produce the desired activated ester **(1.20)**. The pyridinium ring has an electron withdrawing effect that activates the carboxylic acid as an electrophile, and allows nucleophilic attack from the alcohol **(1.10)** to produce an ester **(1.20)**. A stable pyridone compound **(1.21)** is produced as a byproduct. The pyridone compound **(1.21)** is convenient because it will not act as a strong base. It is also water soluble and therefore easily extracted. The ester product formed can then be purified for a very good yield. Mukaiyama's reagent **(1.17)** allowed more mild reaction conditions to occur, as opposed of the harsher conditions in the Williamson-ether synthesis and trichloroacetimidate-promoted esterification reactions.

Scheme 1-5: Esterification using Mukaiyama's Reagent



1.4 Optimized Benzyl Ether Synthesis *via* Oxypyridinium Salts

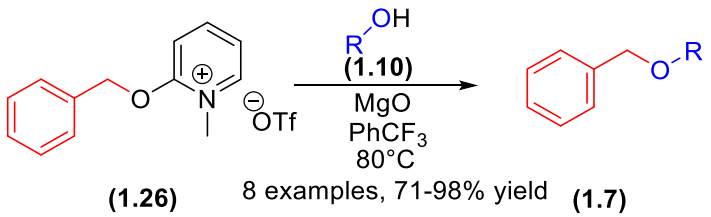
Mukaiyama's reagent **(1.17)** was the inspiration behind the synthesis of the reagent known as 2-benzyloxy-1-methylpyridinium triflate, (BnOPT) **(1.26)** because of the activated nitrogen.[12] BnOPT **(1.26)** allowed for the transfer of benzyl groups under mild conditions **(Scheme 1-6)**. 2-Chloropyridine **(1.22)** and benzyl alcohol **(1.23)** were allowed to stir in toluene to synthesize 2-benzyloxypyridine **(1.24)**. Then using the strong alkylating compound MeOTf **(1.25)**, a methyl group could be transferred to the pyridine nitrogen to synthesize BnOPT **(1.26)**. BnOPT is a white crystalline bench stable solid that is easily prepared, isolated, and stored.[12]



Scheme 1-6: Synthesis of BnOPT

Since the Williamson ether synthesis requires strongly basic conditions, and the trichloroacetimidate-promoted etherification method requires strongly acidic conditions, the relatively neutral method of etherification utilizing BnOPT **(1.26)** has certain advantages for pH-sensitive compounds. BnOPT **(1.26)** was originally designed to convert alcohols **(1.10)** to benzyl ethers **(1.7) (Scheme 1-7)**.[12,13] Optimized conditions included heating the BnOPT **(1.26)** to 83 °C for 24 h in the presence of an alcohol **(1.10)**. The optimized conditions also used MgO as an acid

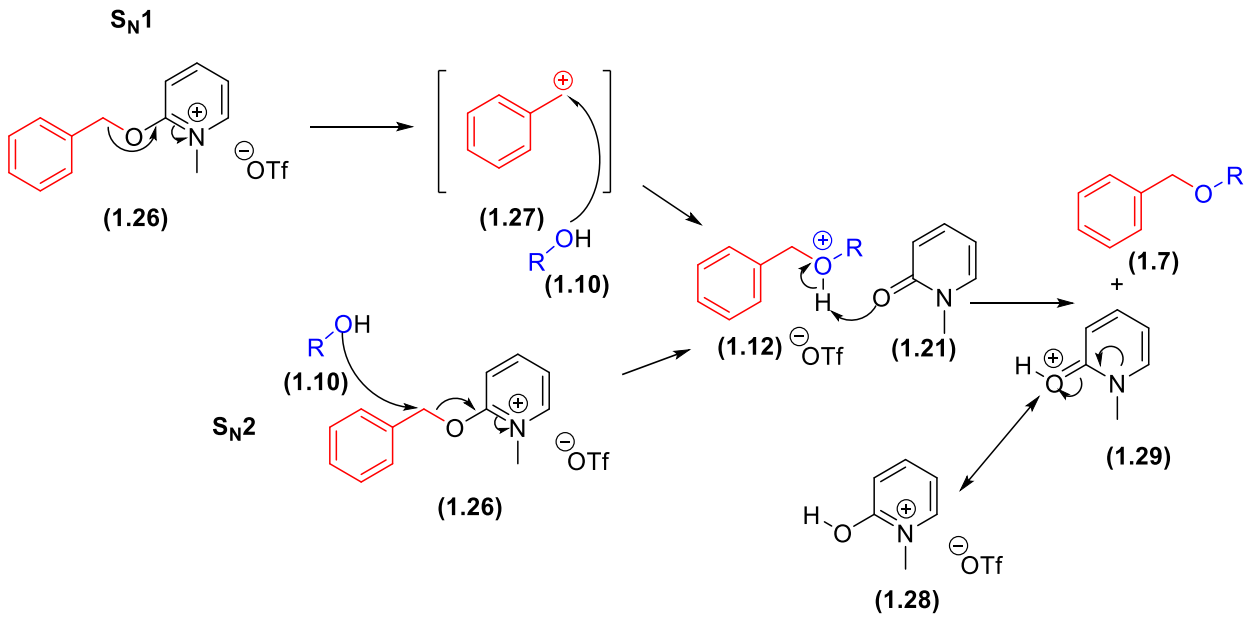
scavenger and trifluorotoluene as the solvent.[12] BnOPT **(1.26)** offered the possibility of synthesizing benzyl ethers **(1.7)** under relatively neutral conditions as opposed to either acidic or basic conditions.



Scheme 1-7: Optimized Conditions for Synthesizing Benzyl Ethers using BnOPT

1.5 S_N1 vs. S_N2 Pathways for Benzyl Transfers

To help facilitate the substrates that could be transferred, it was investigated whether the reaction followed the S_N1 or S_N2 pathway **(Scheme 1-8)**. If the reaction is undergoing a more S_N1-like pathway, then the nucleophilic alcohol is able to attack the benzyl cation **(1.27)**, which would yield the desired benzyl ether after neutralization.[12] An S_N1 pathway would indicate that the resonance-stabilized cation **(1.27)** was generated first, then could be attacked by an alcohol nucleophile **(1.10)** in a second step. An S_N2 pathway would indicate that the nucleophilic alcohol **(1.10)** attacks the benzyl carbon with the concurrent loss of the pyridone leaving group **(1.21)**.[12] The ether product **(1.7)** is formed when the intermediate **(1.12)** is deprotonated by the formed pyridone **(1.21)**.[12]

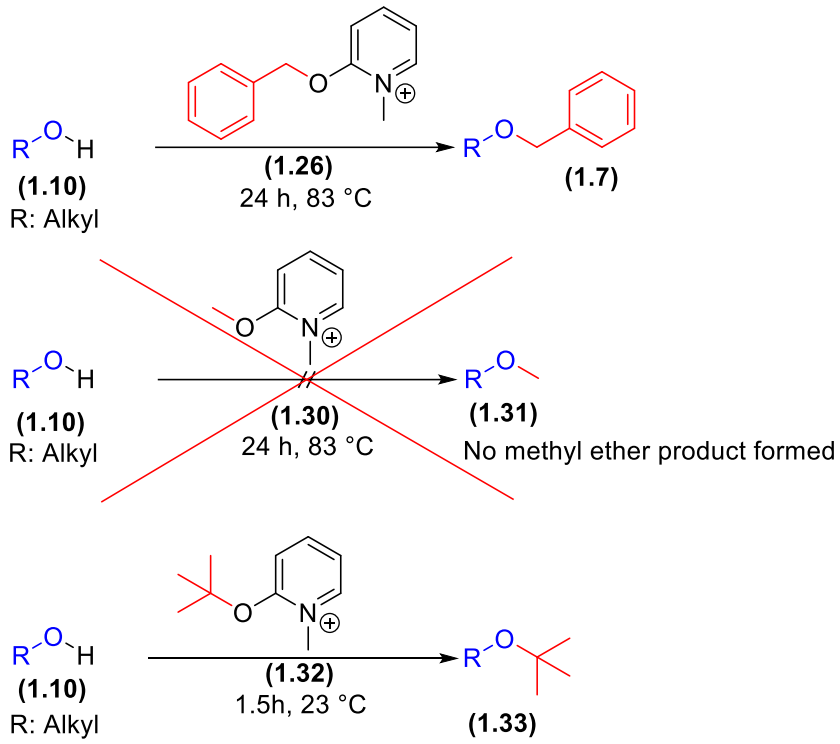


Scheme 1-8: S_N1 and S_N2 Mechanistic Pathways for BnOPT-promoted Etherification

1.6 S_N1 Indicative Experiments

One method of investigating if the mechanistic pathway was more S_N1-like compared to the alternative S_N2 pathway was by synthesizing and comparing the corresponding *t*-butyoxyl **(1.33)** and methoxyl group **(1.31)** *via* corresponding oxypyridinium salts in **Scheme 1-9**. If methylation occurred efficiently, then the reaction mechanism shows significant S_N2 character because the methyl group is not very sterically hindered, which facilitates backside attack. A methyl carbocation is not stable, so it would be unlikely to exhibit S_N1 character if the corresponding product formed. However, if the *t*-butyl group transferred efficiently, then the mechanism is more S_N1-favored because the *t*-butyl group is very sterically hindered, limiting backside attack. The *t*-butyl cation is a relatively stable tertiary carbocation. The mechanism is more likely indicative of a S_N1 pathway. The methyl derivative of BnOPT **(1.26)** resulted in no methyl ether product **(1.31)** under the same conditions as the original benzyl etherification *via* oxypyridinium salts.[12] The reactivity of the *t*-butyl derivative of BnOPT **(1.26)** was also tested,

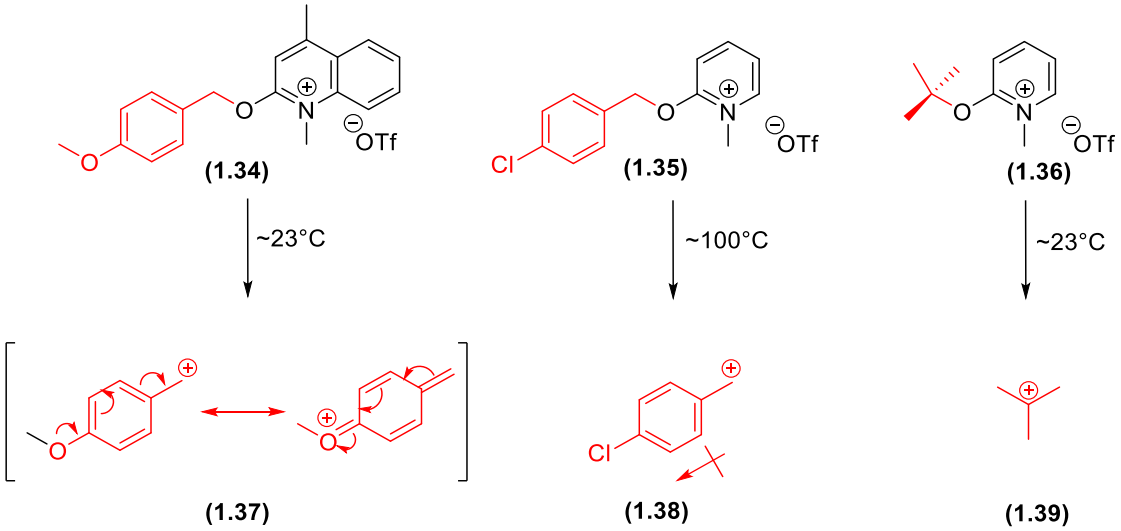
which resulted in the transfer of the *t*-butyl group in 1.5 h at room temperature, proving to be much more reactive than the original BnOPT salt.[14] Therefore, there appears to be more S_N1 pathway character than S_N2 pathway character in the reaction.



Scheme 1-9: Comparing the Reactivity of Arylmethyl and Alkyl Oxypyridinium Salts

Differentially substituted derivatives of BnOPT **(1.26)** could also be used to help determine if the BnOPT pathway was more oriented toward the S_N1 or S_N2 pathway, based on the conditions in which the nucleophile were transferred. Three tested derivatives of BnOPT **(1.26)** including 2-(*p*-methoxybenzyloxy)-methyllepidinium triflate **(1.34)**, 2-(*p*-chlorobenzyloxy)-methylpyridinium triflate **(1.35)**, and 2-*tert*-butyl-1-methylpyridinium trifalte **(1.36)** are summarized in **Scheme 1-10.**[14-16] The methoxy BnOPT derivative is able to transfer the benzyl group at the low temperature of ~23 °C.[15] The stabilized carbocation could contribute to a S_N1-favored pathway. The aryl transfer was facilitated at higher temperatures (100 °C) when using the chloro BnOPT derivative.[16] The chlorine atom is electron withdrawing, which indicates that there is less electron density

around the electrophilic benzylic carbon.[17] Since the chlorine withdrawing carbocation compound **(1.38)** contains an unstable primary carbocation, it was observed that the reaction conditions needed to be harsher (100 °C) than the other BnOPT derivatives tested. The *t*-butyl derivative of BnOPT **(1.36)** was investigated with oxygen nucleophiles, and it was determined that transferring the tertiary stabilized *t*-butyl group **(1.39)** at the lower temperature of 23 °C was efficient.[14] The BnOPT **(1.26)** derivative tests were showing that the most likely mechanistic path BnOPT **(1.26)** was S_N1, mostly due to the success of the transfer of the *t*-butyl group under room temperature and at 1.5 h. The mechanistic pathway is helpful in facilitating the optimized reaction conditions.

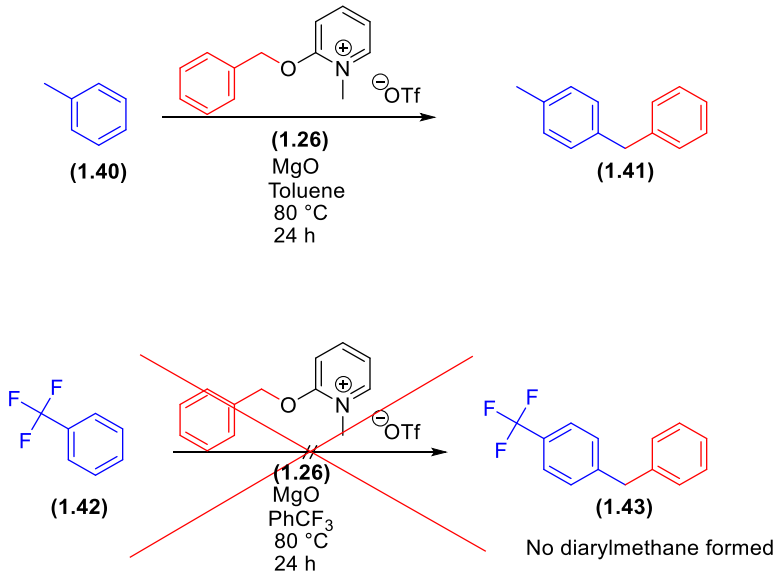


Scheme 1-10: Relative Reactivity of Substituted BnOPT Derivatives

1.7 Solvents Explored in Benzyl Transfer Reactions

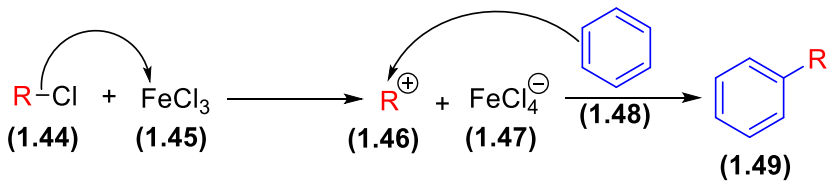
The role of the solvent was also a significant factor in interpreting the mechanism of these reactions. Toluene **(1.40)** and trifluorotoluene **(1.42)** were the two main solvents used for the synthesis of benzyl ethers **(Scheme 1-11)**.[12] The success of $PhCF_3$ and toluene as solvents could be due to aromaticity and pi-pi stacking capabilities between BnOPT **(1.26)** and the solvents. However, toluene **(1.40)** would carry out nucleophilic attacks on the benzyl salt, resulting in benzylated byproducts **(1.41)** through Friedel-Crafts Alkylation. The results showed that the

optimum solvent was trifluorotoluene **(1.42)** due to the lack of benzylated byproducts **(1.43)**, while using the solvent toluene showed said benzylated products. $PhCF_3$ **(1.42)** was utilized as the main solvent used in the reaction.[12]



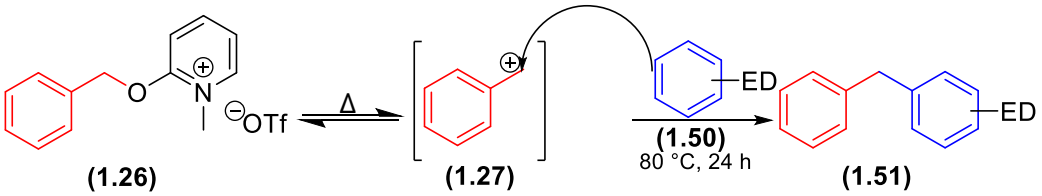
Scheme 1-11: Benzylation of the Solvents Toluene and $PhCF_3$

The -CF_3 group in $PhCF_3$ is electron withdrawing compared to the methyl group in toluene, limiting possible nucleophilic attacks of the aromatic ring. The general Friedel-Crafts reaction is shown in **Scheme 1-12**.[17] The alkylating reagent **(1.44)** would react with a Lewis acid **(1.45)** to generate an electrophile. The aromatic ring **(1.48)** then undergoes nucleophilic attack on the alkylating cation **(1.46)** to synthesize the corresponding product **(1.49)**.



Scheme 1-12: Traditional Friedel-Crafts Reaction

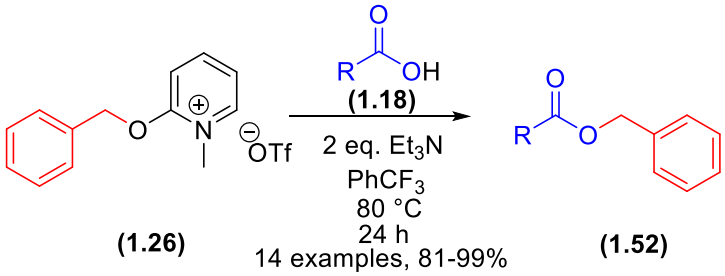
Similarly, when the BnOPT salt **(1.26)** decomposed into a benzyl cation **(1.27)**, then the aromatic ring **(1.50)** carrying an electron donating group potentially attacked the said benzyl cation **(1.27)**. The resultant product was the corresponding benzylated species **(1.51)** in Scheme **1-13**.



Scheme 1-13: BnOPT Salt undergoing Friedel-Crafts Reaction

1.8 Optimized Benzyl Ether Synthesis *via* oxypyridinium Salts

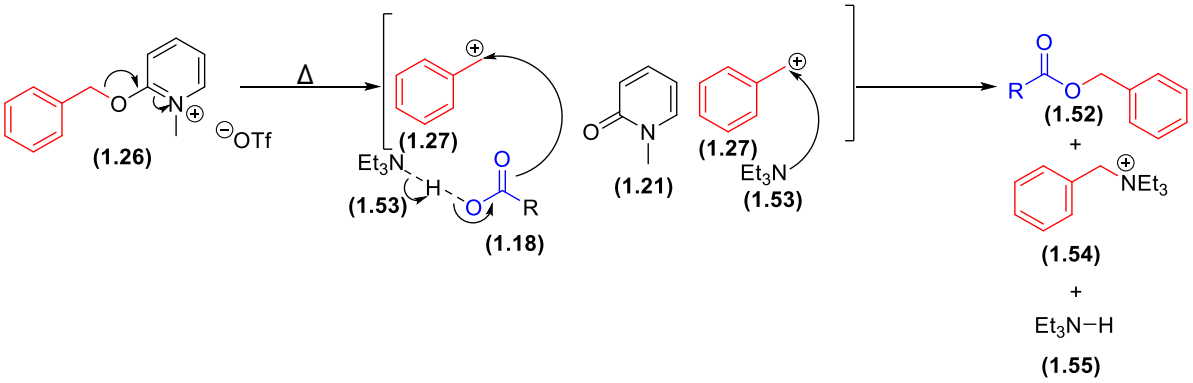
Upon optimization of the method of benzylation of alcohols, other nucleophilic partners were investigated. Specifically, carboxylic acids **(1.18)** were then explored as substrates.[18] Similar to the optimization of benzyl etherification, benzyl esterification used the solvent $PhCF_3$, same temperature, and similar hours **(Scheme 1-14)**. However, the optimization conditions included using two equivalents of trimethylamine as opposed to MgO.[18]



Scheme 1-14: Optimized BnOPT Conditions for Synthesizing Esters

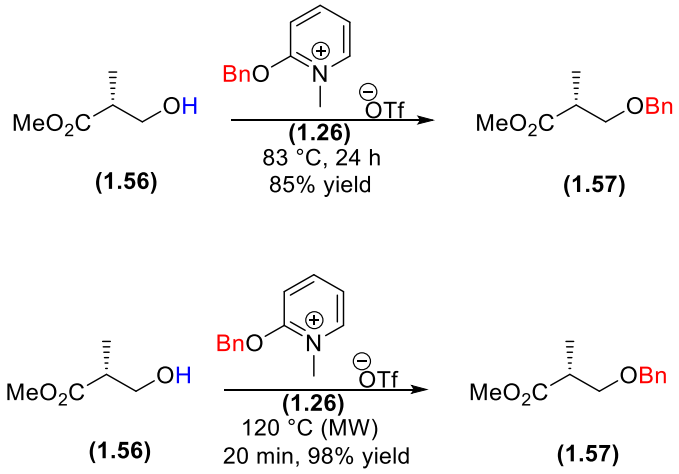
The first equivalent of trimethylamine **(1.53)** was used to activate the nucleophile by coordination to the proton **(1.18)**, while the second equivalent was used to capture any remaining benzyl cations **(1.27)** by nucleophilic attack, suppressing the amount of dibenzyl ether formed.[18] Trifluorotoluene **(1.42)** remained the solvent used, because no formed benzylated byproducts

formed **(1.43).** These reaction conditions produced benzyl esters **(1.52)** in very good to excellent yields **(Scheme 1-15)**.[18]



Scheme 1-15: Mechanism of Synthesizing Benzyl Esters from BnOPT

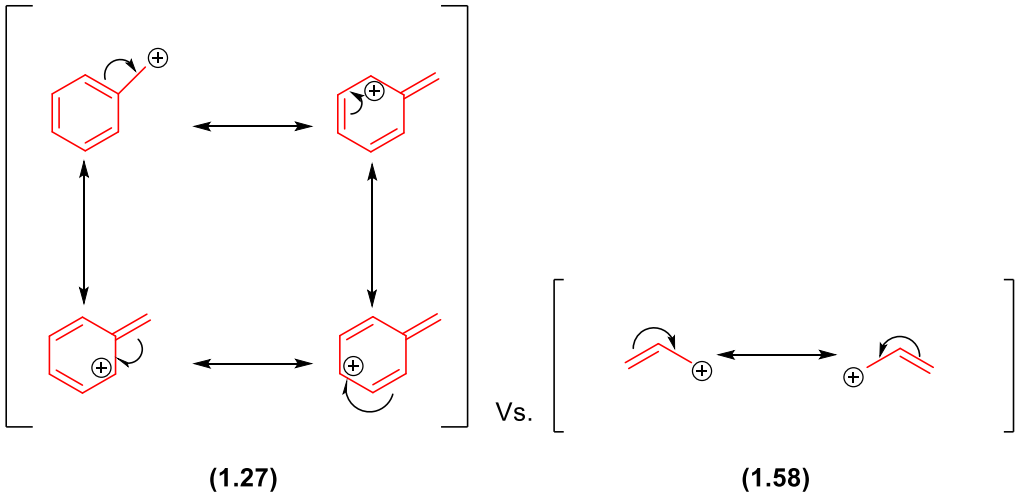
Microwave heating has since been used with BnOPT to synthesize benzyl ethers and esters even more efficiently **(Scheme 1-16)**.[19] The benzylation methodology was able to produce **(1.57)** yields over 90% with primary alcohols **(1.56)** and carboxylic acids **(1.18)**.[19] Microwave heating allowed for the reaction to go to completion in just 20 minutes, whereas conventional heating required 24 h for the reaction to complete.[19]



Scheme 1-16: Benzylation of a 1° Alcohol using MW Heating Compared with Original Thermal Reaction

1.9 Benzyl and Allyl Resonance Stabilized Cations

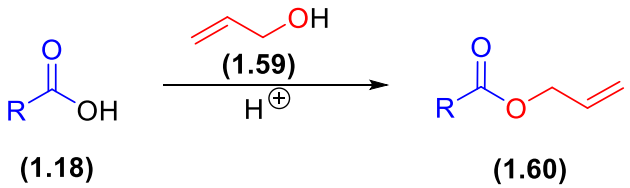
Benzyl and *t*-butyl groups were successfully and efficiently transferred *via* oxypyridinium salts. A functional group with reactivity in between that of a benzyl and *t*-butyl group is an allyl group. Allyl groups are vastly used as protecting groups and can be used in 3,3-rearrangements. The benzyl cation **(1.27)** is more resonance stabilized than the corresponding allyl cation **(1.58)**, indicating the allyl group may be a more difficult group to transfer if the process is truly more S_N1-like **(Scheme 1-17)**.



Scheme 1-17: Resonance Stabilized Benzyl Cation vs. Resonance Stabilized Allyl Cation

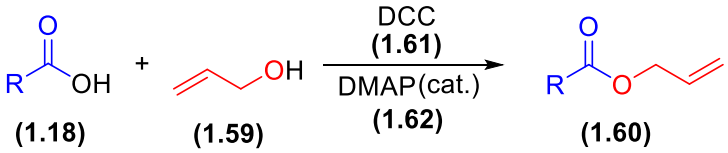
1.10 Prominent Allyl Esterification Methods

Since benzyl groups have been effectively transferred, it became a priority to explore other possible popular protecting groups using similar methodology. Carboxylic acid substrates **(1.18)** have been effectively allylated **(Scheme 1-18)**.[20] Fischer's esterification is one of the popular methods of esterification, but the main imitations include thermodynamic reversibility, slower reaction times, and the acidic conditions could cleave undesired functional groups.[20]



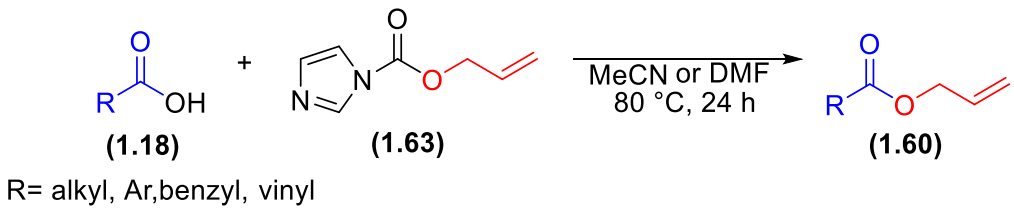
Scheme 1-18: Fischer Esterification Allyl Esters

Steglich esterification is also a well-known esterification reaction. One of the key advantages of Steglich esterification is the conversion of sterically demanding substrates to the desired products.[21] Unlike Fischer esterification, Steglich used dicyclohexylcarbodiimide (DCC) **(1.61)** and 4-dimethylaminopyridine (DMAP) **(1.62)**. DCC **(1.61)** deprotonates the carboxylic acid **(1.18)**.[21] DMAP **(1.62)** potentially acts as an acyl transfer reagent in the reaction **(Scheme 1-19)**. Once the intermediate is formed, then the alcohol is able to add to the carboxylic acid **(1.18)** to form the corresponding allyl ester **(1.60)**.



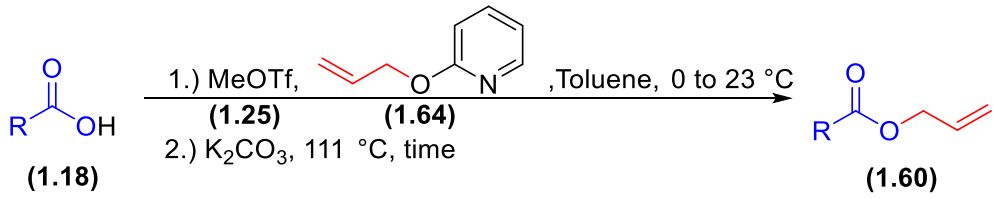
Scheme 1-19: Steglich Esterification Allyl Esters

Another way to facilitate allyl transfer to synthesize allyl esters is the use of imidazole carbamates **(1.63) (Scheme 1-20)**.[22] They are able to facilitate the chemoselective esterification of carboxylic acids **(1.18)**. A carboxylic acid **(1.18)** is added with the imidazole carbamate **(1.63)** in MeCN and DMF to synthesize allyl esters **(1.60)** in very high yields.[22]



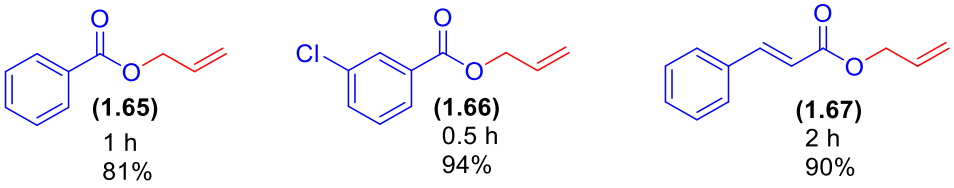
Scheme 1-20: Allyl Ester Synthesis *via* Imidazole Carbamates

Since many esterification methods allowed the transfer of allyl groups to carboxylic acid substrates **(1.18)**, it allowed for the possibility to explore reaction conditions to transfer allyl groups using similar methods that were used to transfer benzyl groups **(Scheme 1-21)**. Carboxylic acids were the ideal substrate to utilize because of the very acidic hydrogen attached to the oxygen, facilitating the deprotonation using a base. The carboxylate could be more involved in the rate limiting step if the reactions is pursuing more S_N2-like character. The carboxylate would be more involved as a nucleophile because it is more reactive and electron rich. Benzyl transfers using BnOPT proved to have significant S_N1-like characteristics. If the esterification using allyl transfer reagents proved more to be S_N2-like, then that would be a significant change in mechanism from using BnOPT as the benzyl transfer agent. The optimized reaction conditions included using the methylated form of 2-allyloxypyridine **(1.64)** as the allyl transfer reagent.[23] The base K_2CO_3 was found to be more efficient in ensuring higher yields, as opposed to using Et_3N during allyl transfer reactions.[23] However, K_2CO_3 was more efficient in consuming the starting materials, but did yield more byproducts. $PhCF_3$ was the optimized solvent for the transferring benzyl groups using BnOPT **(1.26)** because toluene introduced unwanted byproducts synthesized *via* Friedel-Craft reactions **(Scheme 1.3)**.[23] However, using the solvent toluene did not produce any unwanted allylarene byproducts.[23] Toluene **(1.40)** was also a more efficient solvent than trifluorotoluene **(1.43)** due to the elevated temperature, which allowed for the reaction to complete slightly faster.[23]



Scheme 1-21: Allyl Transfer to Carboxylic Acid Substrates

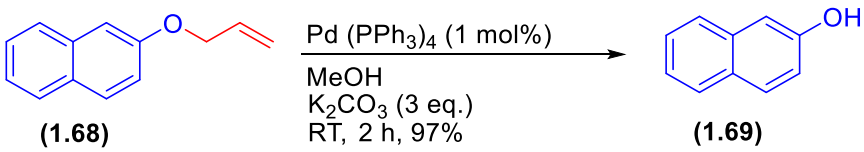
Many substrates were examined, and the reaction proved to yield good to excellent yields in relatively short amount of time **(Scheme 1-22)**.[23] Since allyl transfers to carboxylic acids were optimized, allyl transfer to other substrates could be investigated.



Scheme 1-22: Optimized Allyl Ester Yields

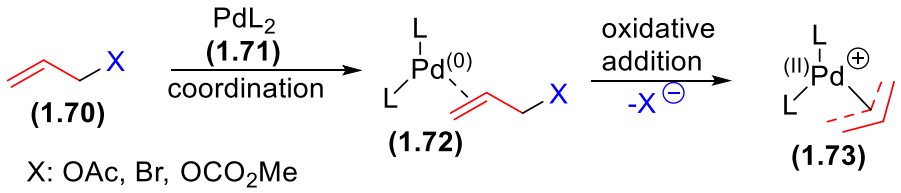
1.11 Deprotection of Allyl Ethers using Palladium Catalysts

Allyl ethers are useful because they can be selectively deprotected using palladium catalysts **(Scheme 1-23)**.[24] One specific method to accomplish selective allyl cleavage is to use a transition metal catalyst, specifically palladium.[24] The allyl ether **(1.68)** is selectively cleaved with the use of palladium to synthesize the corresponding alcohol product **(1.69)**.[24] Selective cleavage is significant because it allows for deprotection of specific groups, which allows for different reactive sites on the molecules to be more reactive towards desired product formations.[24]



Scheme 1-23: Deprotection of Allyl Groups using Palladium Catalyst

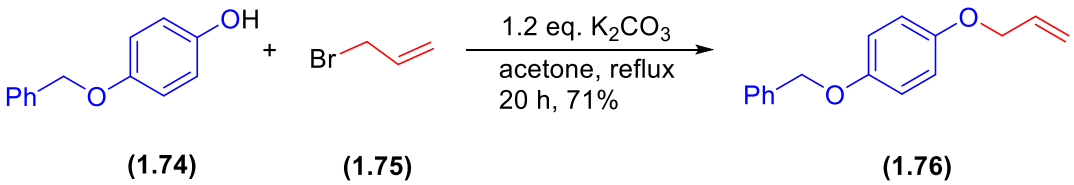
The selective cleavage of allyl groups on allyl ethers is possible when the η^3 π-allyl complex intermediate is formed **(Scheme 1-24)**.[25] This intermediate is significant because it allows for the selective cleavage of allyl groups *via* palladium catalyst. First, the palladium ligand **(1.71)** is able to coordinate with the allyl group on the reagent **(1.70)**, creating the η^2 π-allyl complex **(1.72)**.[25] Then the leaving group is expelled, which synthesizes the η^3 π-allyl complex **(1.73)**.[25]



Scheme 1-24: Formation of the η³ π-Allyl Intermediate *via* Palladium Catalyst

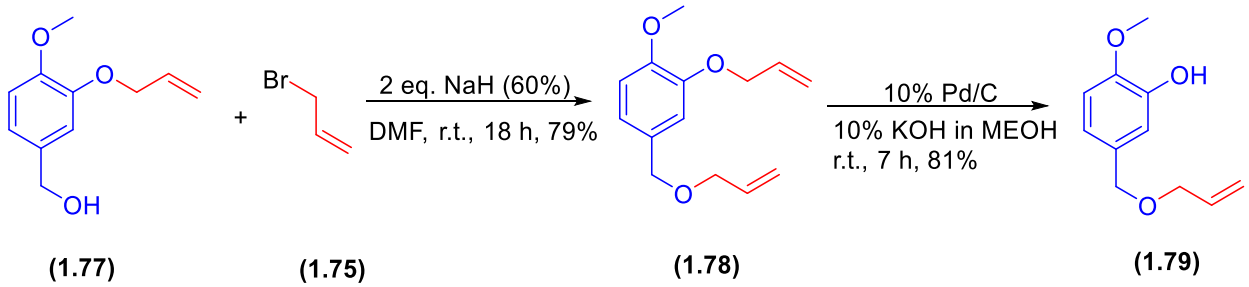
1.12 Prominent Allyl Etherification Methods

There are a variety of methods that allow the transfer of the allyl groups using allyl bromide **(1.75)** to synthesize the corresponding allyl ether **(1.76)**, under relatively mild conditions **(Scheme 1-25**).[26] The K_2CO_3 allows for the deprotonation of the phenolic hydrogen **(1.74)**.[24] The electron-rich oxygen is then permitted to do a S_N2 attack on the electrophilic carbon to synthesize the corresponding allyl ether **(1.76)**.[26] Allyl bromide **(1.75)** transfers proved to be a widely used due to simplicity of the reaction. However, the yields could be improved using different methodology.



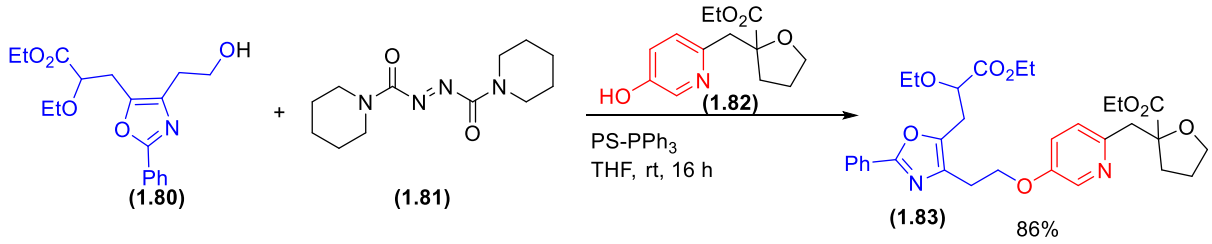
Scheme 1-25: Allyl Etherification using Allyl Bromide

The allyl bromide **(1.75)** is used to transfer the allyl group **(Scheme 1-26)**.[26] Sodium hydride is the stronger base used to deprotonate the alcohol.[26] Palladium is able to selectively cleave the allyl group attached to the phenolic oxygen **(1.78)** due to the phenolic anion resonance stabilization.[26]. Allyl transfer and cleavage methods *via* said conditions proved to be relatively efficient in reaction time and yields.[26]



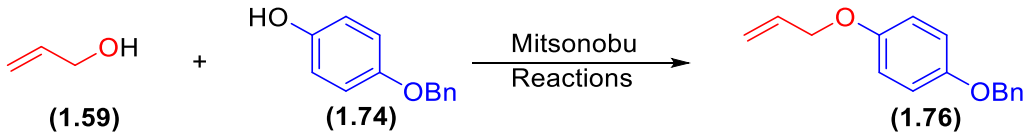
Scheme 1-26: Allyl Etherification and Selective Cleavage

A common method to synthesize phenolic ethers is the Mitsunobu reaction **(Scheme 1-27)**.[27] Mitsunobu reactions are well known for their method for the inversion of stereogenic centers in product synthesis **(1.83)**.[27] Unlike the Fischer esterification reaction, the oxygen moiety in the product does not come from the alcohol reagent **(1.80)**.[27] Instead, the oxygen moiety comes from the phenolic hydrogen on compound **1.82**.[27] 1,1-(Azodicarbonyl) dipiperidine (ADDP) **(1.81)** is utilized because it allows for a stronger base intermediate to occur.[27].



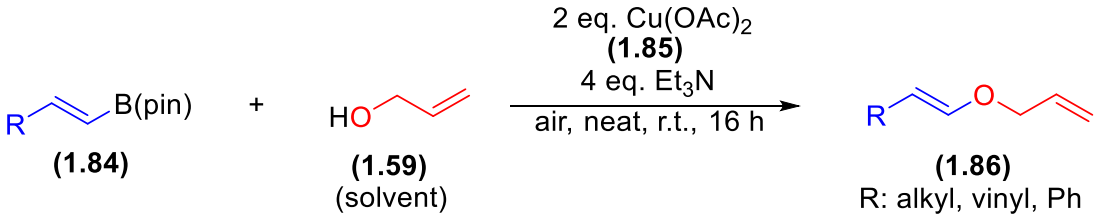
Scheme 1-27: Phenyl Ether Synthesis using Mitsunobu Conditions

Mitsunobu reactions were not only efficient in phenyl ether synthesis, the reaction conditions also allowed for the transfer of allyl groups **(Scheme 1-28)**.[27] The product is shown to be an allyl ether **(1.76)** using Mitsunobu reaction conditions.[27] The product oxygen moiety originates from the allyl alcohol reagent **(1.59)**, as opposed to the phenyl oxygen moiety **(1.74)**.[27] Mitsunobu reactions have been a very popular method of allyl ether formation. However, there are other widely used methods as well.



Scheme 1-28: Allyl Etherification using Mitsunobu Conditions

One possible method to facilitate the transfer of allyl groups includes copper-promoted coupling of vinyl boronates **(1.84)** and the allyl alcohol solvent **(1.59) (Scheme 1-29)**.[28] The B(pin) (Bis(pinacolato)diboron) protecting group protects the R-substituted vinyl group until the allyl transfer occurs.[28] The solvent allyl alcohol **(1.59)** plays a major role in the nucleophilic attack to synthesize the corresponding allyl ethers.[28] The stereospecific and stereoselective copper-promoted esters **(1.85)** allow for the synthesis of the corresponding allyl ethers **(1.86)** in very good yields.[28] The main advantage of this reaction is that it is done at room temperature. The reaction being done under mild conditions is a significant insight to other possible mild condition reactions.



Scheme 1-29: Allyl Etherification using Nucleophilic Solvents

1.13 Research Goals

Current transfer methods of allyl groups to alcohols and phenols were invested in literature, but it was investigated whether these transfers could occur under relatively mild conditions *via* oxypyridinium salts. Benzyl groups have been successfully transferred to carboxylic acid and alcohol substrates with great success.[12,18] methyl groups were unable to be transferred, but *t*-butyl were successfully transferred *via* oxypyridinium salts.[14] If the mechanism is more S_N1 favored, then an allyl group could be used as a possible group to transfer due to its reactivity being in

between that of a *t*-butyl group and methyl group. Allyl transfers were also optimized for carboxylic acid substrates *via* oxypyridinium salts.[23] Since an allyl cation is less resonance stabilized than a benzyl cation, the possibilities of transferring the allyl group could remain to be more difficult and require harsher conditions. Investigating the possibilities of transferring allyl groups to other possible substrates, specifically phenols and alcohols, were investigated.

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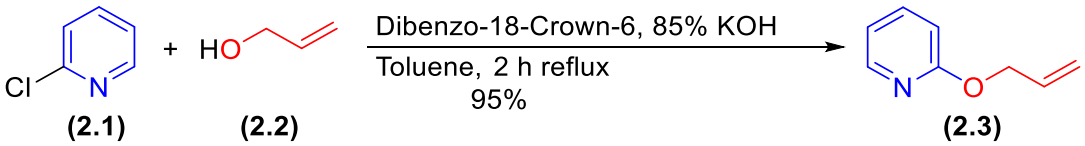
Chapter II: The Investigation of Allyl Etherification Methods *via* Oxypyridinium Salts

2.1 Synthesizing 2-Allyoxypyridine and its Corresponding Salt

The goal of this project was to explore the possibilities of transferring allyl groups to phenols and alcohols *via* oxypyridinium salts. The first step was to synthesize a reagent that allowed for the transfer of allyl groups. Then understanding the possible mechanisms by which the allyl salt could undergo was useful in determining possible allyl etherification methods. Then completing different reaction conditions to transfer allyl groups were tested for phenol and alcohol substrates.

To be able to design efficient methods of allyl etherification, a salt analogous to BnOPT was designed to transfer allyl groups. 2-Allyloxypyridine **(2.3)** was produced using 2-chloropyridine **(2.1)**, allyl alcohol **(2.2)**, dibenzo-18-Crown-6, 85% KOH, and toluene **(Scheme 2-1)**.[1] As opposed to the benzyl derivative, the allyl derivative forms a more stable species. The 2-allyloxypridine **(2.3)** precursor can then undergo methylation to produce its corresponding salt.[1]

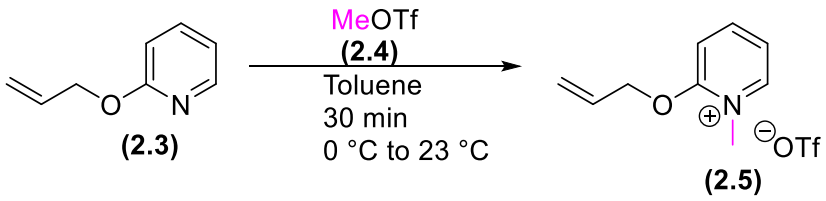


(2.1) **(2.2)** **(2.3)**

Scheme 2-1: Synthesis of 2-Allyloxypyridine

Similar to the BnOPT salt, 2-allyloxy-1-methylpyridinium triflate (AMPT) **(2.5)** was designed to act as the allyl transfer reagent. The nitrogen on the pyridine ring from the 2-allyoxypyridine **(2.3)** was alkylated using MeOTf **(2.4)**, which enhanced the electrophilicity of the compound **(Scheme 2-2)**. However, when using AMPT **(2.5)**, the reaction occurs more efficiently *in situ*. AMPT **(2.5)** was difficult to weigh out because of its amorphous-like consistency.[1] Upon

completing the synthesis of AMPT **(2.5)**, the salt was ready to be investigated in allyl etherification reactions.

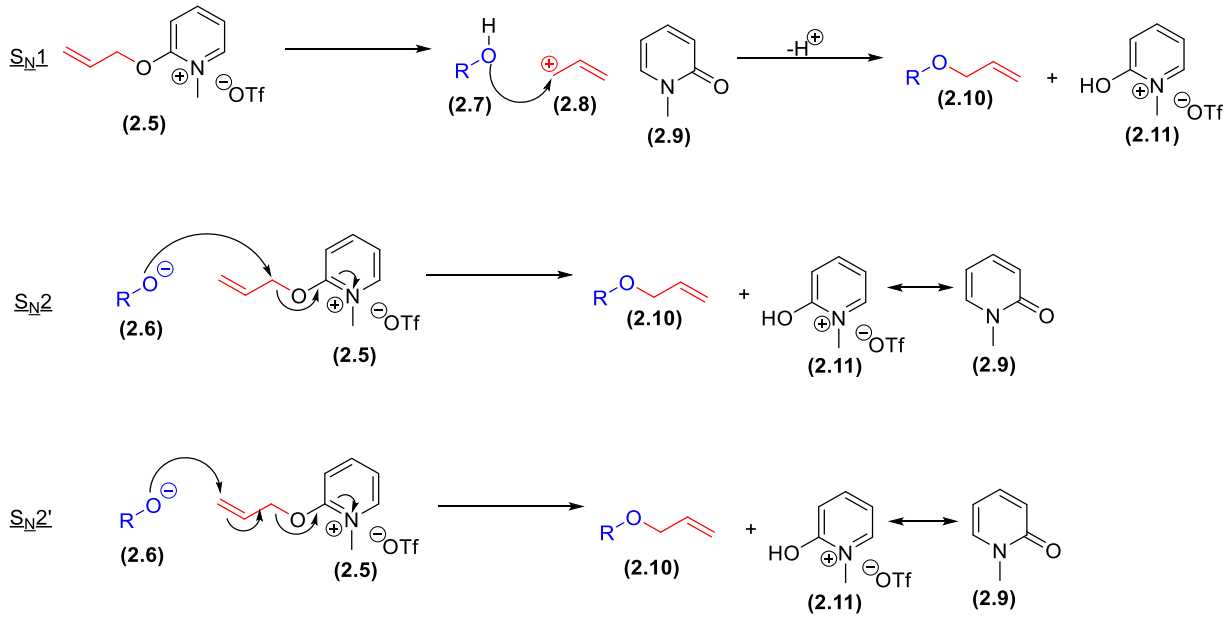


Scheme 2-2: Formation of 2-Allyoxy-1-methylpyridinium Triflate (AMPT)

2.2 Predicted Mechanism of Allyl Etherification *via* Oxypyridinium Salts

Before exploring the transfer of allyl groups, it was important to consider the possible mechanisms that the allyl group transfers undergo. Understanding the mechanism can help determine the most efficient methods of allyl etherification. Unlike the benzyl transfer reactions, there appears to be three possible mechanistic possibilities for the transfer of the allyl group *via* oxypyridinium salts. S_N1, S_N2, and S_N2' were concluded to be the main prospects for the mechanistic possibilities **(Scheme 2-3)**.[1] In an S_N1 reaction, the allyl salt **(2.5)** decomposes. Then the alcohol nucleophile **(2.7)** proceeds to attack the cationic allyl group **(2.8)**, resulting in the allyl ether product **(2.10)** being produced, as well as the pyridine **(2.9)** and its tautomer **(2.11)**. In an S_N2 reaction, the reagent **(2.6)** attacks the carbon adjacent to the oxygen on the allyl salt **(2.5)**, forming the products **(2.10)**. Uniquely, S_N2' may also be prevalent, which indicates that the carbon on the allyl group furthest from the oxygen is being attacked **(2.5)**, causing activation of the compound to synthesize the products **(2.10)**. In the original BnOPT reactions, the mechanism favored more S_N1-characteristics, which means the activation of the nucleophile influenced the reaction less than in an S_N2-like pathway.[2,3] An S_N2-favored pathway would indicate that the activation of the nucleophile matters more in the mechanism because S_N2 favored reactions include the nucleophile in the rate limiting step. If the allyl salt was easier to decompose, then the reaction

would show S_N1-like characteristics.[1] Understanding the most likely mechanisms of the allyl transfer reaction could reward us with a much more elaborate and comprehensive understanding of these reactions. Rate studies including tagging the hydrogens and carbons could also prove useful in determining the mechanism.



Scheme 2-3: Possible Allyl Transfer Mechanisms of S_N1, S_N2, and S_N2'

2.3 Investigating Allyl Transfers to Alcohols *via* Oxypyridinium Salts

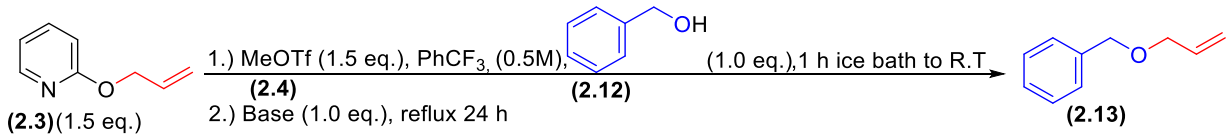
To initiate the study of the formation of allyl ethers a series of reactions were screened using a variety of conditions differing in temperature, time, and bases. The theoretical yield for all reactions allyl etherification reactions were explored using 75 mg. Benzyl alcohol **(2.12)** was chosen as the main substrate to begin screening because its corresponding allyl ether **(2.13)** was easily interpretable *via* ^{1}H-NMR. The bases examined included K_2CO_3, MgO, $NaHCO_3$, Et_3N, and pyridine. MgO, K_2CO_3, and $NaHCO_3$ are more insoluble bases than Et_3N or pyridine. K_2CO_3 is a base that has been shown to work well in allyl transfer to carboxylic acids and benzyl transfers to carboxylic acids.[1,2] Et_3N and pyridine are both nitrogen-containing organic soluble bases. MgO

was a base proven useful in the transfer of benzyl groups to alcohols.[3] K_2CO_3 is a stronger base with a pKa of 10.3, than $NaHCO_3$, which has two pKa values of 10.3 and 6.4.[4] The main goal was to find a base for the reaction that contains the optimal conditions for both solubility and basicity.

In addition to testing various bases, other reaction conditions had to be explored. The solvent $PhCF_3$ would be utilized because it was the most effective solvent for the benzylation of alcohols and carboxylic acids. The stoichiometric ratio was kept the same for each trial of reactions. The 2-allyloxypyridine **(2.3)**, MeOTf **(2.4)**, benzyl alcohol **(2.12)**, and $PhCF_3$ were placed into a flask and set into an ice bath for 1 h and then warmed up to room temperature to produce the AMPT **(2.5)** *in situ*. Then the base was added and the reaction was allowed to stir at 104 °C for 24 h before being worked up. The crude yields showed low product to starting material ratios, indicating that the AMPT **(2.5)** may not be as soluble as BnOPT under similar conditions.

To have an efficient reaction, the goal was to convert most of the starting material to product as possible, while the reaction went to reflux for 24 h or less. **Table 2-1 (**entries **1** and **2)** prove that magnesium oxide works most efficiently. However, the reaction remained inconsistent between trials and the reactions provided only about a 50 percent product conversion after 24 h. Although 50 percent of product conversation is a good start, many possibilities remained to increase the reaction yields. The reason that the reaction did not convert all the starting material to product could be due to the AMPT (**2.5**) being less soluble, the bases not being soluble enough, and the AMPT (**2.5**) salt not decomposing to the corresponding allyl cation if the reaction wasn't undergoing S_N1 conditions. If the salt or bases were not soluble enough in the reaction, then methods to increase solubility would be incorporated.

Table 2-1: Investigating Allyl Ether Product Formation by Varying Bases

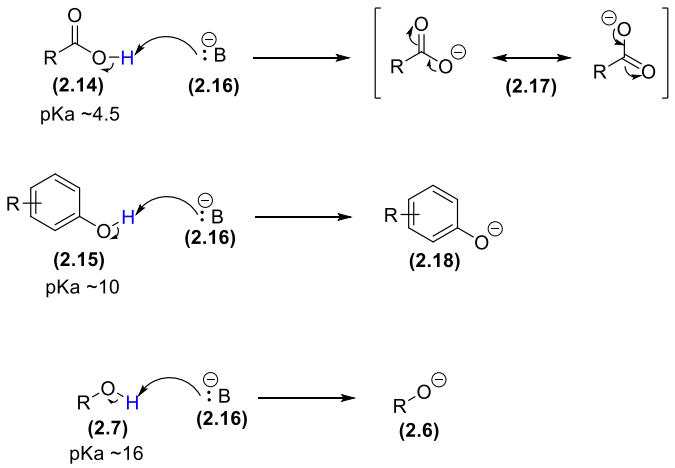


Entry	Bases	Solvent	Crude recovery (%)*	Crude 2.13/2.12 Ratio	Pure yield (%)
1	**MgO**	**$PhCF_3$**	**>100**	**2:0.6**	**<26%**
2	**MgO**	**Toluene**	**>100**	**2:1.3**	**---**
3	K_2CO_3	$PhCF_3$	>100	2:5.7	---
4	$NaHCO_3$	$PhCF_3$	>100	2:3.1	---
5	Et_3N	$PhCF_3$	>100	2:1.7	<<25%
6	Pyridine	$PhCF_3$	>100	2:1.5	---

* Calculated as the weight of the crude isolated product mixture

2.4 Investigating Allyl Transfers to Phenols *via* Oxypyridinium Salts

Due to the low product conversions in the initial base screening, other methods to improve the reaction yields were explored. Since alcohols **(2.7)** have a higher pKa value (~16) than carboxylic acids (~4.5) **(2.14)**, deprotonation of carboxylic acids is preferred over alcohols **(Scheme 2-4)**.[5-7] Therefore, to be able to efficiently activate the nucleophile, it became rational to attempt to optimize the reaction conditions for phenols **(2.15)** due to the lower pKa value (~10), before moving back to alcohols **(2.7)**.[5-7]

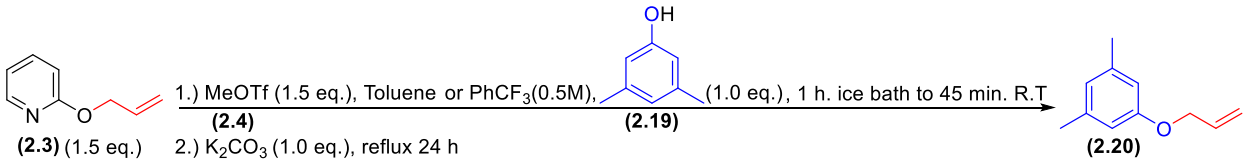


Scheme 2-4: A Comparison of Substrate pKa Values

3,5-Dimethylphenol **(2.19)** was chosen as the initial substrate because of the simplicity in interpreting the ^{1}H-NMR peaks with its corresponding allyl ether **(2.20)**. The allylation of phenols examined were similar to the allylation of alcohols, except toluene, instead of $PhCF_3$, was used as the solvent. Since toluene and $PhCF_3$ yielded similar yields in the previous allylation of carboxylic acid reactions, both solvents were utilized in exploring the allylation of phenols.

Base screenings were already investigated for alcohol substrates, and a new base screening was done for the phenols **(Table 2-2)**. The goal was to have all the starting material convert to product and to be able to efficiently recover the product. The most successful base was K_2CO_3 (entries **3** and **4**). The base K_2CO_3 worked more efficiently than any other bases, activating the nucleophile to allow the reaction to occur. The solvents $PhCF_3$ and toluene (entries **3** and **4**) appeared to yield similar results to one another. The crude recoveries were over 100% and the product was purified with moderate difficulty. The insoluble base and salt remained an issue. Also, to limit the competition of methylation occurring on the substrate, it was seen best to add the substrate after the salt was formed. Then have the reaction refluxing before adding the base. The phenol substrate would not be forced to compete with the salt formation process, even though the procedure would be slightly more difficult because an extra step was added.

Table 2-2: Yields for Allyl Ethers Synthesized using Various Bases and the Solvents Toluene and $PhCF_3$



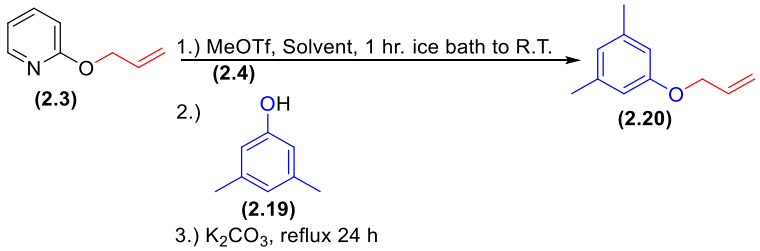
Entry	Bases	Solvent	Crude Recovery (%)	Crude 2.20/2.19 Ratio	Pure Yield (%)
1	MgO	$PhCF_3$	>100%	2 to 80	---
2		Toluene	>100%	2 to 82	---
3	**K_2CO_3**	**$PhCF_3$**	**>100%**	**2 to 2.0**	**---**
4		**Toluene**	**>100%**	**2 to 1.7**	**~20%**
5	$NaHCO_3$	$PhCF_3$	>100%	2 to 58	---
6		Toluene	>100%	2 to 50	---
7	Et_3N	$PhCF_3$	>100%	2 to 45	---
8		Toluene	>100%	2 to 51	---
9	Pyridine	$PhCF_3$	>100%	2 to 60	---
10		Toluene	>100%	2 to 55	---

* Calculated as the weight of the crude isolated product mixture

Since solubility still appeared to be an issue due to the insoluble base and salt, different solvents were allowed to heat to reflux, which were investigated as ways to enhance solubility of the salt. The new reaction conditions would utilize the most effective base from the initial base screening, K_2CO_3. In **Table 2-3**, 1,4-Dioxane (entry **1**) resulted in no salt formation because the freezing point of the solvent 1,4-Dioxane is above 0 °C, which meant the desired reaction would not occur because there was no salt formation. 1,2-Dichloroethane (entry **2**) showed that some product is formed, but not at a high crude recovery. A mixture of toluene and 1,2-dichloroethane (entry **3**) was tested to investigate if a ratio of the two solvents could pose higher crude recoveries, but that only seemed to lower the efficiency of the reaction. Nitromethane (entry **4**) was able to synthesize the salt, but contained very minute amounts of crude product. N-methyl-2-pyrrolidinone

(NMP) (entry **5**) was examined to observe if higher temperatures could solubilize the salt, but no salt was formed, and therefore this solvent couldn't be used to test higher temperatures. Chlorobenzene (entry **8**) was observed because it has similar electronic properties as a solvent to $PhCF_3$, but chlorobenzene has a higher boiling point temperature. However, chlorobenzene still appeared inefficient in synthesizing high crude product yields. Xylenes were (entry **9**) used to see if product synthesis could be examined more efficiently with higher temperatures, but product synthesis was nonexistent. The results were surprising because the solvent xylenes only differ from toluene in that it contains an extra methyl group on the ring. Entries **6** and **7** showed that trifluorotoluene and toluene remained to be the most efficient solvent. This phenomenon was not surprising, considering the optimized allylation of carboxylic acids utilized the solvent toluene.

Table 2-3: Solvent Screening for the Synthesis of Allyl Ethers



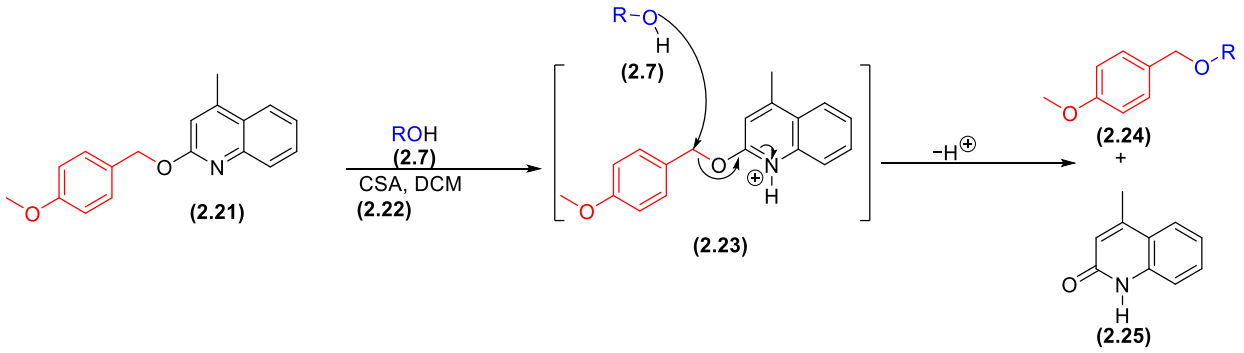
Entry	Solvents	Ice bath/R.T. (h)	Temperature (°C)	Crude 2.20/2.19 Ratio	Pure Yield (%)
1	1,4-Dioxane	Freezing point too high	N/A*	N/A*	---
2	1,2-Dichloroethane	1 h to R.T.	83	6:25 (30%)	---
3	50/50% Toluene/1,2-Dichloroethane	1 h to R.T.	111	6:123 (6%)	---
4	Nitromethane	1 h to R.T	100	6:146 (4%)	---
5	N-methyl-2-pyrrolidinone(NMP)	1 h to R.T. (no salt)	N/A*	N/A*	---
6	**Toluene**	**1 h to R.T.**	**111**	**2:1 (66%)**	**~50%**
7	**$PhCF_3$**	**1 h to R.T.**	**104**	**1:1 (50%)**	**---**
8	Chlorobenzene	1 h to R.T.	131	6:38 (13.6%)	---
9	Xylene	1 h to R.T.	138	No product	---

* No salt was formed, and therefore the reaction was tested no further

The reaction was inconsistent in producing the desired products because the base and salt were still not very soluble under current conditions. Although the new reaction conditions improved the current yields, the goal remained to increase yields under efficient reaction conditions. At this point, K_2CO_3 and the solvents toluene and $PhCF_3$ were the most efficient reaction conditions screened.

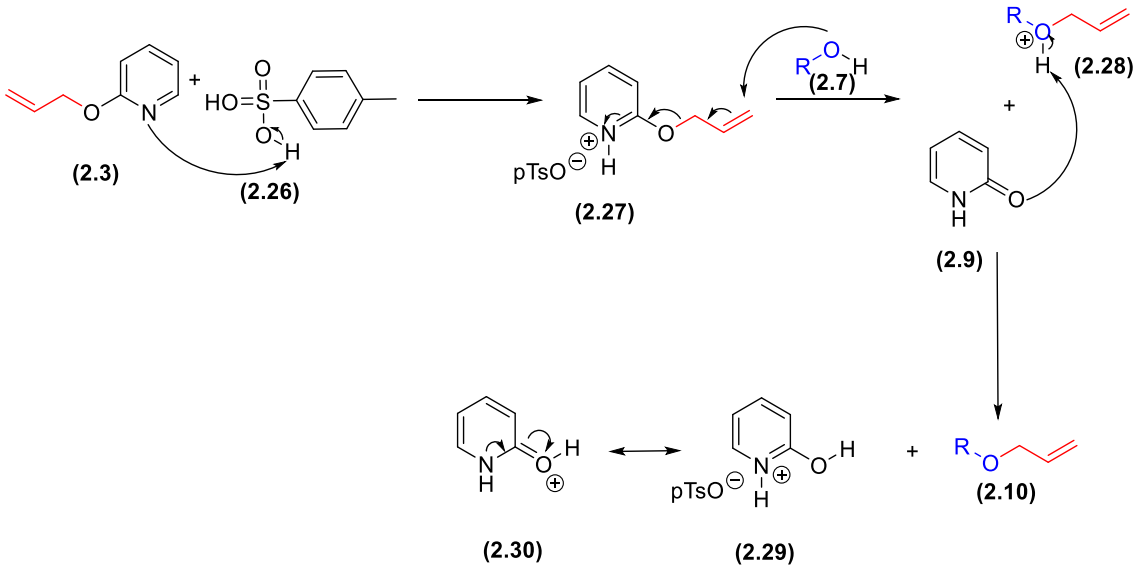
The previous reactions were all completed under mildly basic conditions. There were no immediate or obvious routes of reaction screenings under mild conditions. However, using acids as catalysts became a possibility in synthesizing the desired allyl ether products. Paquette used the following reaction under acid-catalyzed conditions **(Scheme 2-5)**.[8] Similarly, acid-catalyzed reactions were also done to optimize the transfer of PMB groups to alcohols using BnOPT.[9] This method was the inspiration for transferring allyl groups to alcohols using acid-catalyzed reactions. However, the salt Paquette used decomposed much more efficiently than the AMPT **(2.5)** salt, as AMPT **(2.5)** is less reactive, specifically as a cation precursor. The following reaction indicates the *para*-methoxybenzyl lepidine ether **(2.21)** being activated by the camphorsulfonic acid catalyst **(2.22)**, allowing the neutral alcoholic nucleophile **(2.7)** to attack the benzylic carbon **(2.23)**.[8]

2.5 Investigating Allyl Transfers to Alcohols under Acid-catalyzed Reactions



Scheme 2-5: Formation of PMB Ether under Acid-catalyzed Conditions[8]

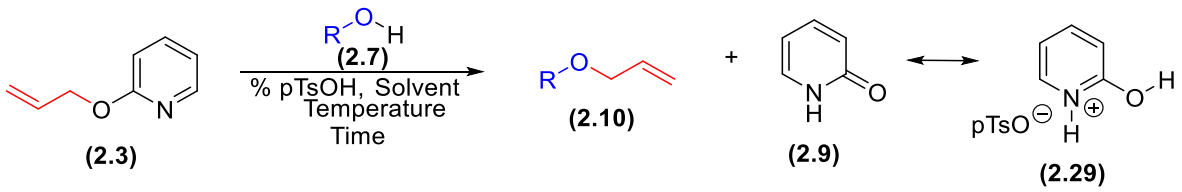
Paquette's successful reaction conditions for synthesis of PMB-ethers led us to determine the alternative route of acid-catalyzed reactions utilizing 2-allyloxypyridine **(2.3) (Scheme 2-6)**.[8] Although using camphorsulfonic acid **(2.22)** would be ideal for direct comparison (Paquette's reactions), the convenient organic acid catalyst used was *para*-toluene sulfonic acid **(2.26)** due to its availability in our laboratory. The mechanism of the proposed reaction may involve the activation of the pyridine nitrogen by protonation from the acid. Then the alcohol **(2.7)**, as nucleophile, could attack the allyl carbon adjacent (or furthest) to oxygen atom **(2.27)** to produce the allyl ether **(2.10)** and pyridine products **(2.9)** after protonation.



Scheme 2-6: Possible S_N2' Mechanism of Acid-catalyzed Reaction

A variety of reaction conditions were explored by varying solvents, temperature, catalyst ratio, and time while monitoring percent conversation **(Table 2-4)**. These acid-catalyzed conditions proved unsuccessful in the conversion of the alcohols **(2.7)** to their corresponding allyl ethers **(2.10)**. However, the reaction in toluene at reflux (entry **11**) proved to show both starting material and a newly generated allyl species. The appearance of the said allyl species is not completely characterized, but it is notable that it is not the desired product.

Table 2-4: Acid-catalyzed Reactions under Varying Conditions



Entry	Substrate	Solvent	Temperature (°C)	Time (h)	Catalyst Loading	Crude Product Conversion
1	Benzyl Alcohol	DCM	R.T.	96 h	100% pTsOH	No product
2	Benzyl Alcohol	DCM	R.T.	96 h	10% pTsOH	No product
3	1-Phenyl-2-propanol	DCM	R.T.	96 h	10% pTsOH	No product
4	Geraniol	DCM	R.T.	96 h	10% pTsOH	No product
5	Benzyl Alcohol	DCM	Reflux	72 h	10% pTsOH	No product
6	1-Phenyl-2-propanol	DCM	Reflux	72 h	10% pTsOH	No product
7	Benzyl Alcohol	Toluene	R.T.	96 h	10% pTsOH	No product
8	1-Phenyl-2-propanol	Toluene	R.T.	96 h	10% pTsOH	No product
9	Benzyl Alcohol	Toluene	50 °C	96 h	10% pTsOH	No product
10	1-Phenyl-2-propanol	Toluene	50 °C	96 h	10% pTsOH	No product
11	**Benzyl Alcohol**	**Toluene**	**Reflux**	**96 h**	**10% pTsOH**	**50% Byproduct***
12	1-Phenyl-2-propanol	Toluene	Reflux	96 h	10% pTsOH	No product

* Reaction produced significant allyl species unrelated to product

The product under the harshest conditions (entry **11**) revealed newly formed peaks (5.92 ppm) that were prevalent on the ^{1}H-NMR, but were not desired product peaks (**Figure 1**). After acid-catalyzed reactions did not prove any noticeable product formation, it became pertinent to try to obtain the desirable allyl ether products *via* mild conditions once again.

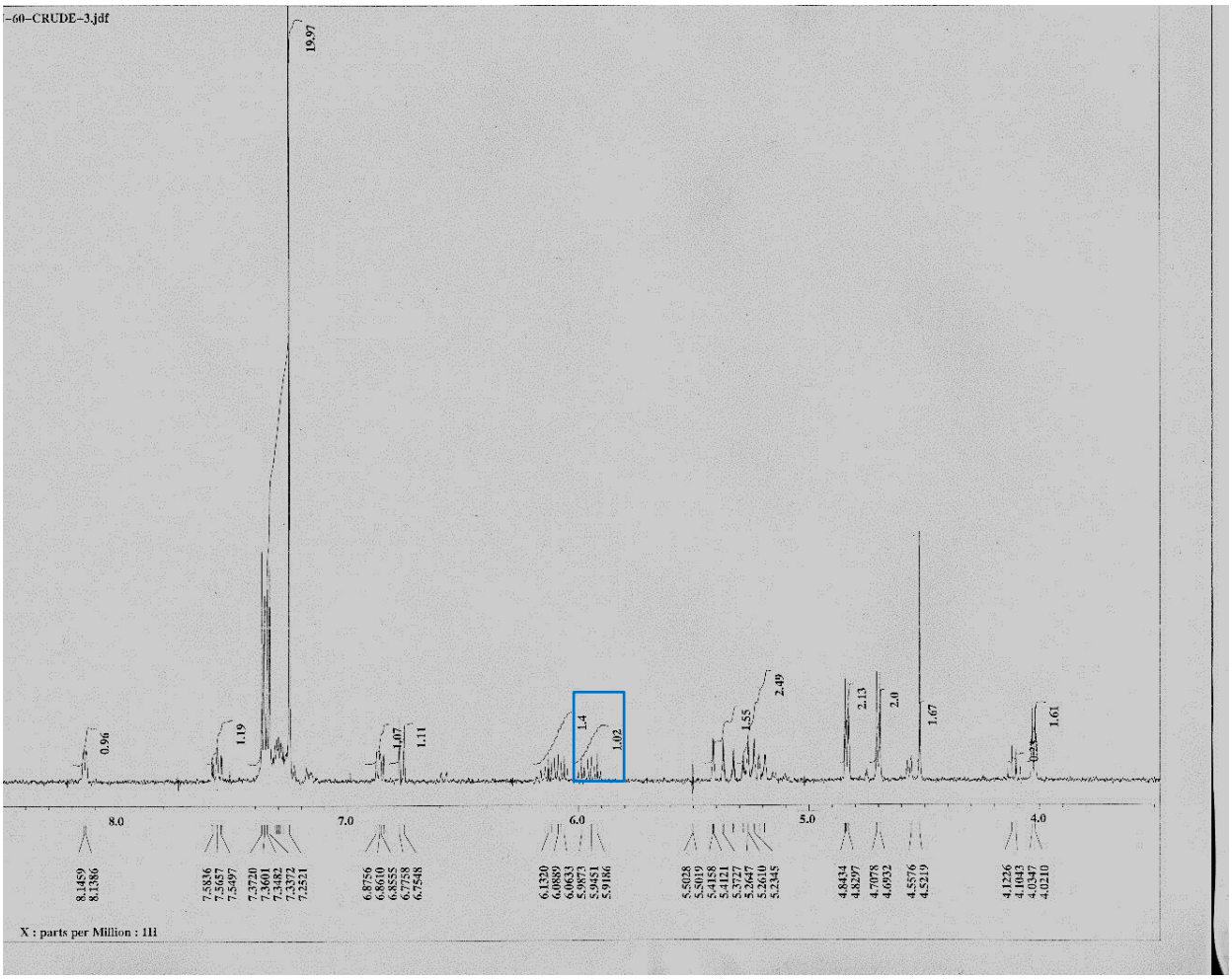
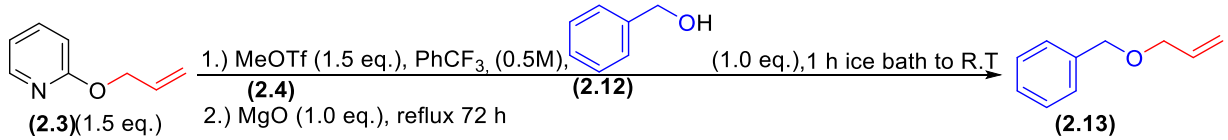


Figure 1: Uncharacterized Allyl Byproduct (Entry 11)

2.6 Investigating Advancements in Allyl Transfers to Alcohols

When exploring alcohol substrates **(2.12)** once again, it became apparent that using 5 mL microvials gave very poor product **(2.13)** completions yields, if any at all **(Scheme 2-7)**. After using larger flasks, there was a difference in percent of crude recovery obtained. Several trials were tested to explore how the flask size influences product yields. All other reaction conditions remained constant throughout the trials. As flask size increases, there was more product being formed. After 5 mL microvials proved to show low product conversions, higher flask sizes were used.



Scheme 2-7: Synthesizing Allyl Ethers under Current Optimized Conditions

25 ml flasks proved to allow the reaction to go to completion after 72 h, but the reaction outcome was inconsistent. Three peaks were significant peaks to search for in the reactions. The peak around 5.95 ppm indicated the single hydrogen on the allyl group, the peaks around 5.34 ppm and 5.23 ppm indicated the two hydrogens attached to the double bond. The final peak is around 4.04 ppm describing the hydrogens adjacent to the oxygen on the allyl group. As the surface area increased, more product formed because the product peaks assumed correct hydrogen integrations. After numerous 5 mL microvial (**Figure 2a**) vs. 25 mL flask comparisons (**Figure 2b**), the vials never gave promising product conversions after 24 h, while the flasks inconsistently gave higher crude product recoveries after 24 h.

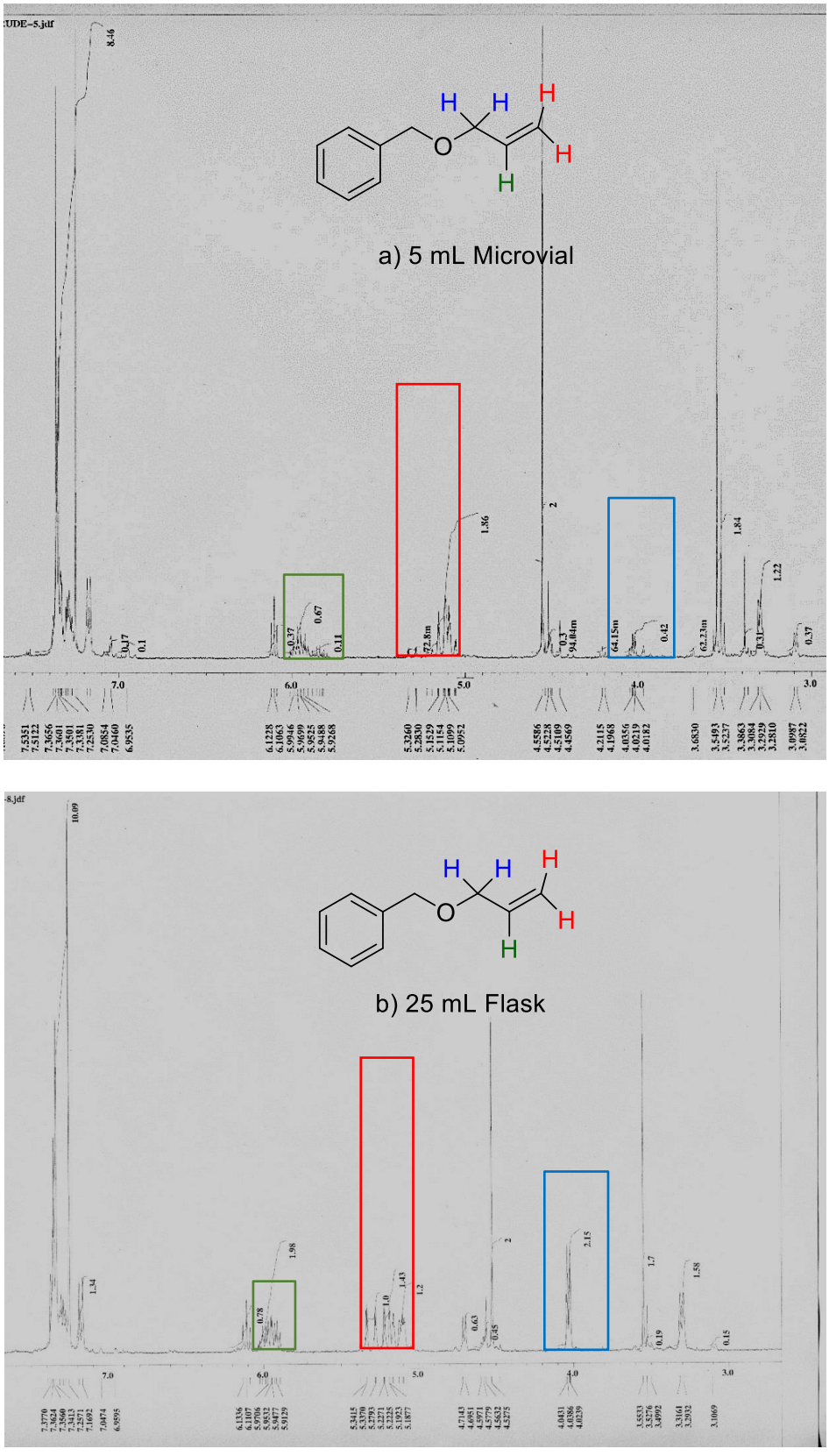
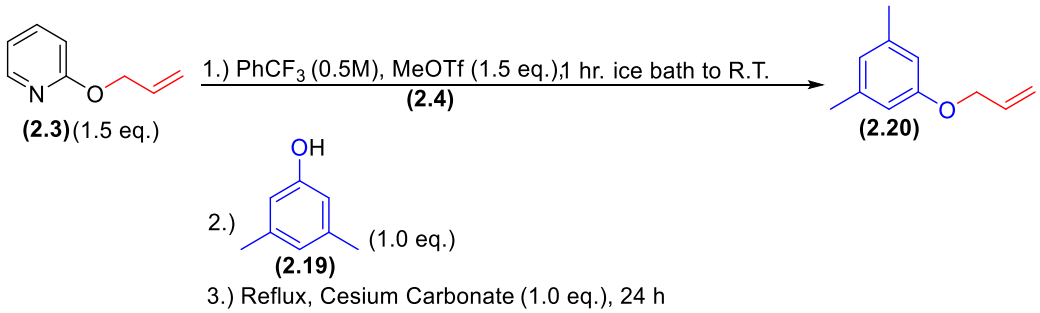


Figure 2: Allyl Ether Synthesized in a) 5 mL Microvial and b) 25 mL Flask

2.7 Investigating the Optimal Bases in Allyl Transfers to Phenols

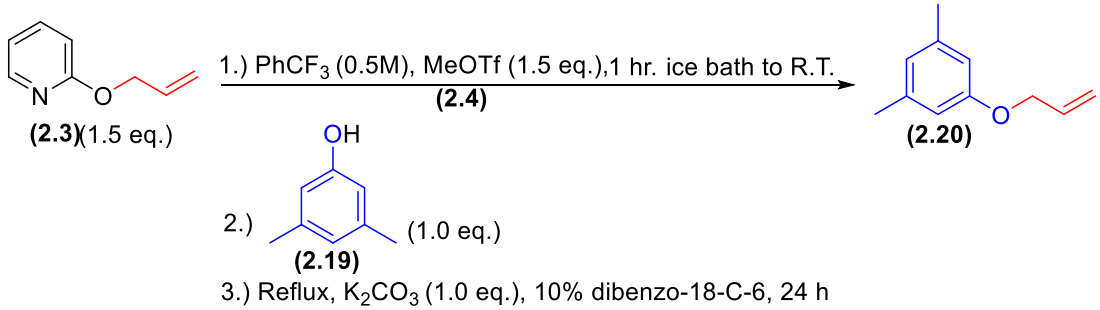
After noticing that flasks made a significant impact on the product yields, new conditions on the phenol substrates **(2.15)** were explored. The product **(2.20)** obtained using 3,5-dimethylphenol **(2.19)** was significant because the carbons on the methyl groups allowed determination of how much starting material to product ratio was occurring. This is possible because the product contains 6 hydrogens in the same region (about 2.26 ppm) on the ^{1}H-NMR spectra, and any more hydrogens overlapping the same peak could be reasonably deemed starting material or byproduct. The product peak at about 4.50 ppm represents the hydrogens connected to the allyl group carbon adjacent to the oxygen. The single allyl hydrogen has a peak around 6.04 ppm, and the two hydrogens connected to the ally double bond are at the peaks around 5.42 ppm and 5.25 ppm. The salt and base were still insoluble, so it became pertinent to find ways to solubilize the reaction conditions. Soluble bases such as Cs_2CO_3 could be used, and adding a catalyst with potassium carbonate could be used to increase solubility. A trial of using Cs_2CO_3 as the base was then explored **(Scheme 2-8)**.



Scheme 2-8: Synthesizing Allyl Ethers using Cs_2CO_3

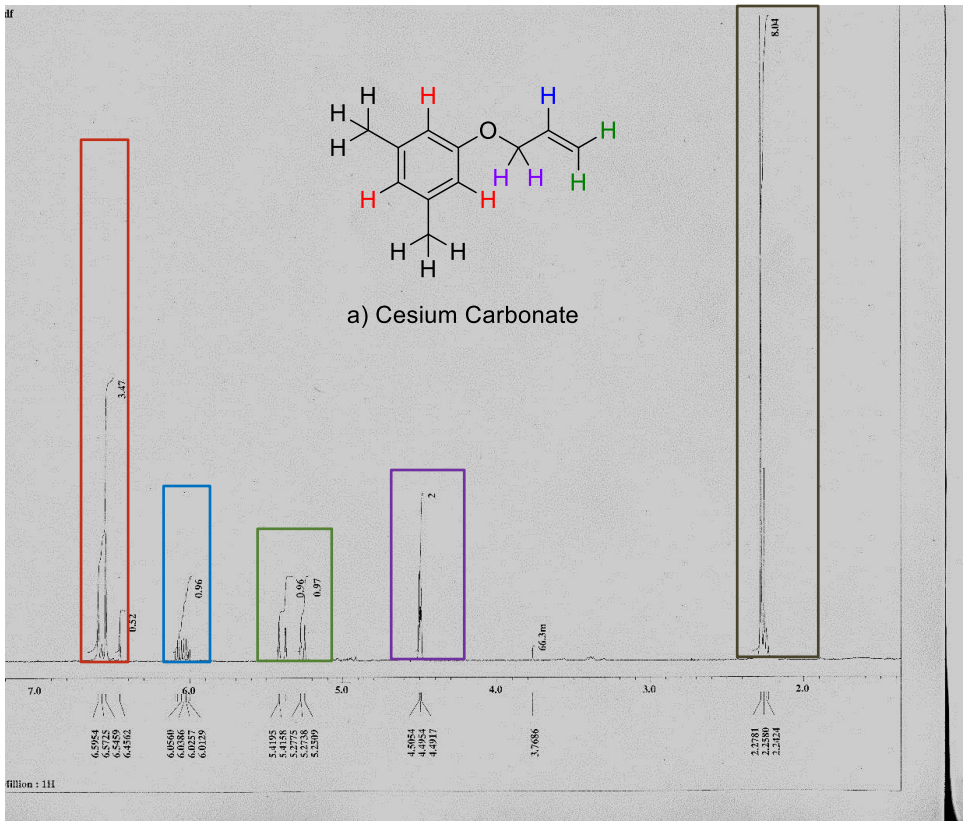
CS_2CO_3 is a soluble base, but K_2CO_3 is less soluble. One way to solubilize K_2CO_3 is to add a catalyst. The catalyst chosen for the trials was dibenzo-18-C-6 because it is known to be an efficient soluble catalyst and is easily available. K_2CO_3 and 10% of dibenzo-18-C-6 were used in

the reaction **(Scheme 2-9)**. Also, a 25 mL round bottom flask was used to hold the reactants during the reaction.



Scheme 2-9: Synthesizing Allyl Ethers using K_2CO_3 and Catalyst

The spectra for **Figure 3a** shows about 75% of crude product conversion using Cs_2CO_3. The new peak at 4.50 ppm shows the desired product peak. The peak at 4.50 ppm shows the two hydrogens on the allyl carbon adjacent to the oxygen. The crude product recovery is calculated by dividing the product peaks over the total peaks. For example, if the peak at about 2.26 ppm showed an integration of 8, along with other product peaks, then the assumption is 6 of those 8 hydrogens is product. Using cesium carbonate as the base increased product yields substantially, and with consistency. However, while using K_2CO_3 with a catalyst, the crude product conversion significantly improved as well. The crude conversion was shown to be approximately 90% **(Figure 3b)**. The next goal was to identify whether using cesium carbonate, or using K_2CO_3 with the additional of a catalyst, was more efficient and consistent for product synthesis.



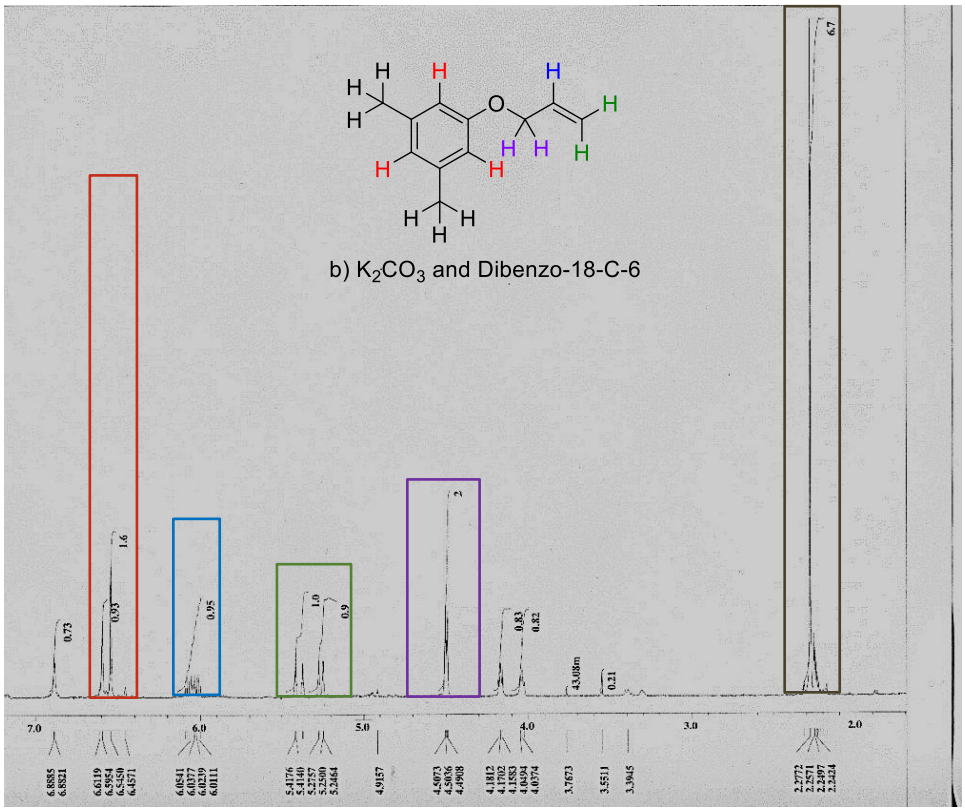
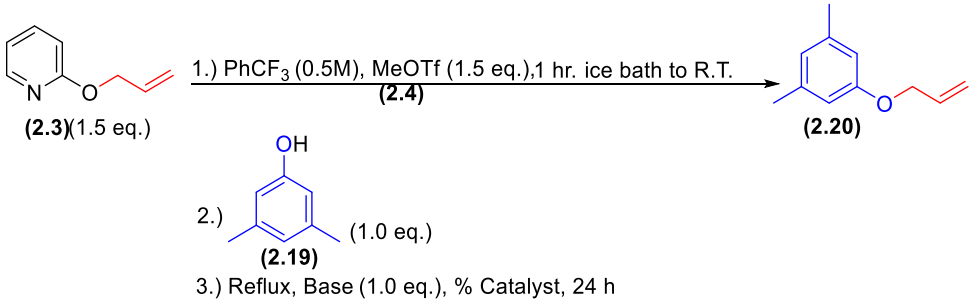


Figure 3: Allyl Ether Spectra using a) Cs_2CO_3 and b) K_2CO_3 and Dibenzo-18-C-6

Further experiments testing base, percent catalyst, and size of flask could be observed to optimize the conditions. In **Table 2-5**, entries **2** vs**. 7** shows that K_2CO_3 with catalyst led to a higher product yield than Cs_2CO_3. When further testing the reaction conditions for the percentage of catalyst, entries **1** vs. **6** showed that 1% of dibenzo-18-C-6 worked just as efficiently as 10% of catalyst. When using vials, entries of **2** vs. **5** and **6** vs. **8** showed that the crude product conversions were far below the crude product conversions of the reactions done in flask. Reasons of higher yields were possibly due to surface area and more even heating throughout (entry **7**).

Table 2-5: Experimenting Various Conditions for Allyl Etherification



Entry	Base	Percent Catalyst	Size of Flask (mL)	Crude Product 2.20/2.19 Ratio	Pure yield (%)
1	K_2CO_3	10%	25 mL flask	6:1.01	70%
2	Cs_2CO_3	0%	25 mL flask	6:2.21	55%
3	Cs_2CO_3	0%	25 mL flask	6:2.61	---
4	Cs_2CO_3	0%	25 mL flask	6:2.32	---
5	Cs_2CO_3	0%	5 mL microvial	6:12.75	---
6	K_2CO_3	1%	25 mL flask	6:0.91	85%
7	K_2CO_3	2%	25 mL flask	6:0.47	92%
8	K_2CO_3	1%	5 mL microvial	6:9.13	---
9	K_2CO_3	1%	5 mL microvial	6:7.39	---
10	K_2CO_3	2%	50 mL flask	6:0.56	---

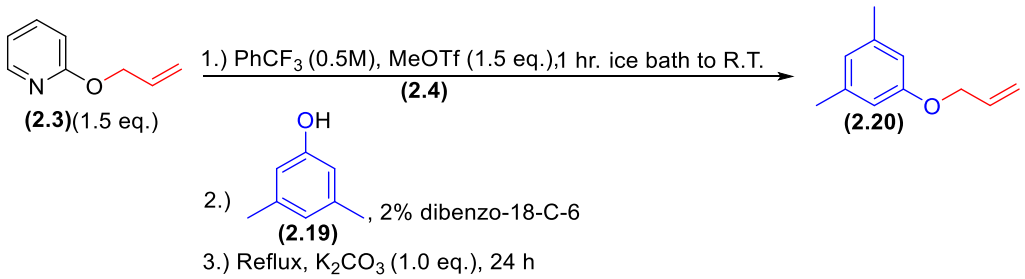
The allylation reaction that worked most efficiently was using a 25 mL flask, and with the base K_2CO_3 and the addition of 1% or 2% catalyst (entries **6** and **7**). The reaction conditions using Cs_2CO_3 as a base did provide a lower diversity of byproduct formation compared to the K_2CO_3 with catalyst reactions. However, K_2CO_3 with catalyst reactions had the catalyst easily separated

via flash column chromatography, as the catalyst precipitated after loading. Based on the results, the optimized reaction conditions would include K_2CO_3 and catalyst as opposed to Cs_2CO_3. Since the conditions were optimized, exploring surface area in more detail could reveal the influences of surface area on the reaction.

2.8 Investigating Surface Area in Allyl Transfers to Phenols

In **Table 2-6**, many experiments were performed to test the impact of different sized flasks. 25 mL flasks proved better than 10 mL flasks (entries **2** vs. **3** and **Figure 4b-c**), which proved more efficient than 5 mL microvials (entry **1** and **Figure 4a**). When using a 50 mL flask (entry **4**), the results showed little difference than utilizing a 25 mL flask. It was important to have even heating throughout the vessel. The influences of the flask size started to diminish when using 50 mL flasks as opposed to 25 mL flasks.

Table 2-6: Experimenting Surface Area Influences for Allyl Etherification



Entry	Size	Crude 2.20/2.19 Ratio	Pure Product (%)
1	5 mL Microvial	6:20.37	---
2	10 mL Flask	6:3.63	---
3	25 mL Flask	6:0.47	82%
4	50 mL Flask	6:0.56	---

The following ^{1}H-NMR spectra shows the product peaks, such as 5.42 ppm or 4.50 ppm, are greater as surface area is increased over the duration of 24 h. Figure **4** shows more product appears in flasks with greater surface area. 5 mL microvials had little crude product conversion,

10 mL flasks had significantly greater crude product conversion, and 25 mL flasks proved to have the most product conversion (**Figure 4a-c)**.

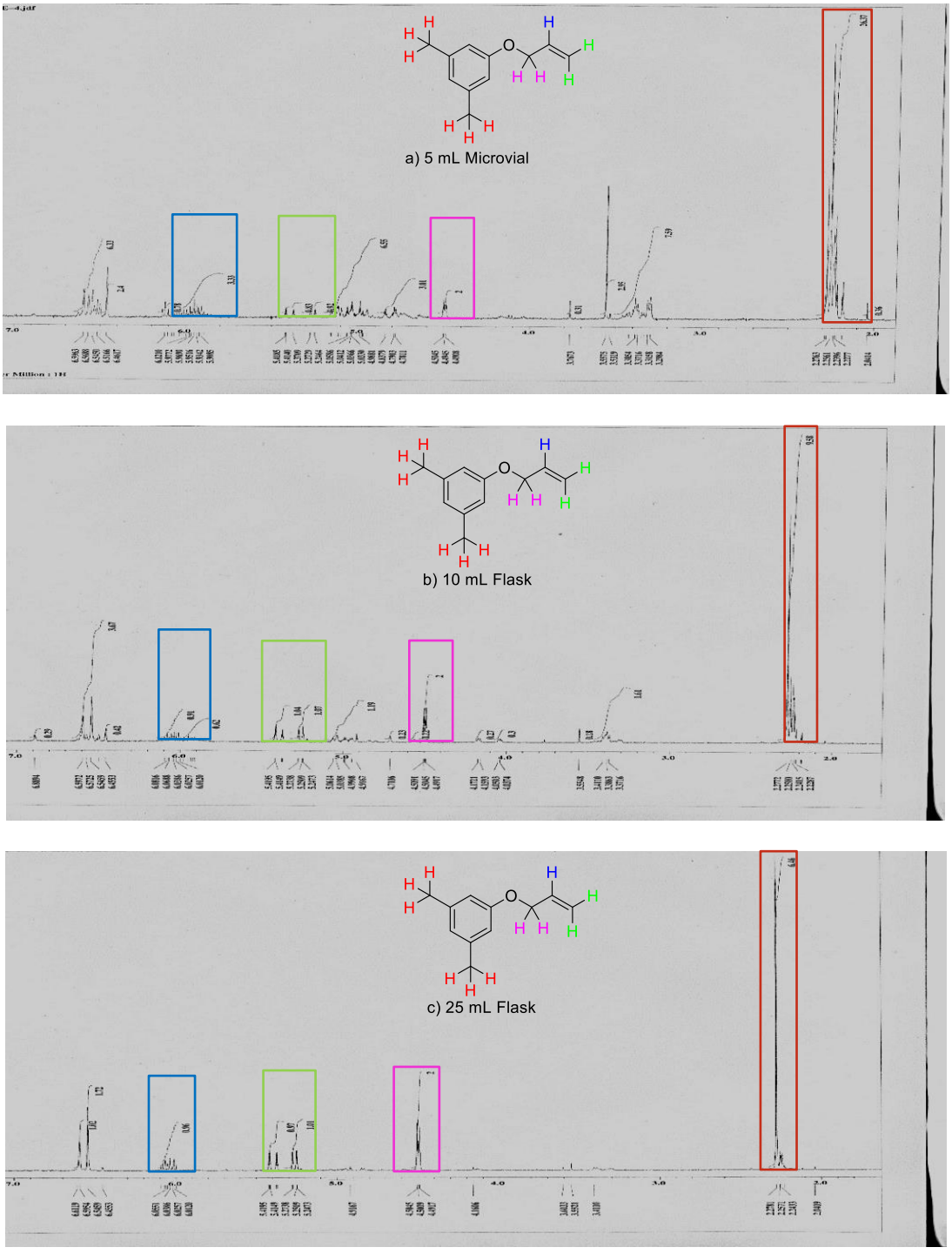
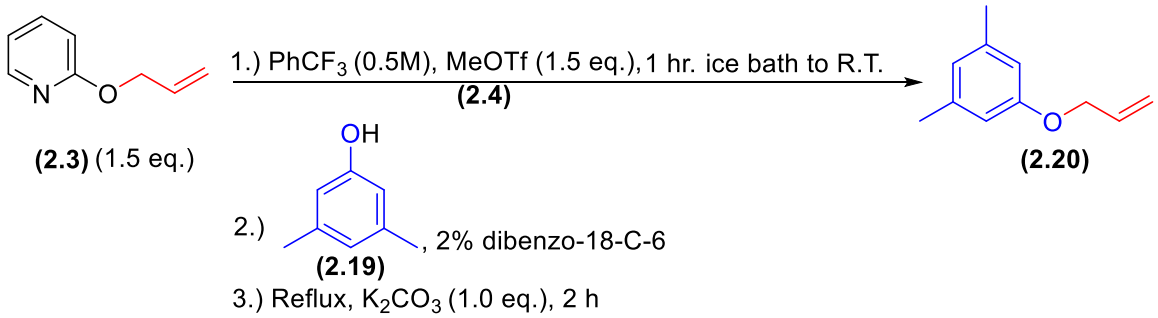


Figure 4: Allyl Ether Synthesized in a) 5 mL Microvial, b) 10 mL Flask, and c) 25 mL Flask

2.9 Optimized Allyl Transfers to Phenols

With the improved conditions using potassium carbonate and catalyst as the main way to solubilize the reaction for higher product **(2.20)** yields in hand, it was useful to test ways to add the reagents in a more efficient way to increase the product yields. It was decided to use less $PhCF_3$ to form the salt. Using the solvent $PhCF_3$ to solubilize both the substrate and the 2% catalyst in a vial was most efficient. The homogenous mixture was then transferred to the 25 mL reaction flask *via* syringe. Then any remaining species found in the vial or syringe and needle was washed with a small amount of $PhCF_3$ and transferred to the flask. 2% catalyst was used for these trials due to the small yields (.075g). This ensured that all of the catalyst enters the flask. Although crude product **(2.20)** conversions were as high as 95% in less than an hour, it was best to allow the reaction to run for 2 h for all substrates, so the more difficult substrates would also be completely converted to products **(Scheme 2-10)**. The reaction of allylating phenols was optimized.

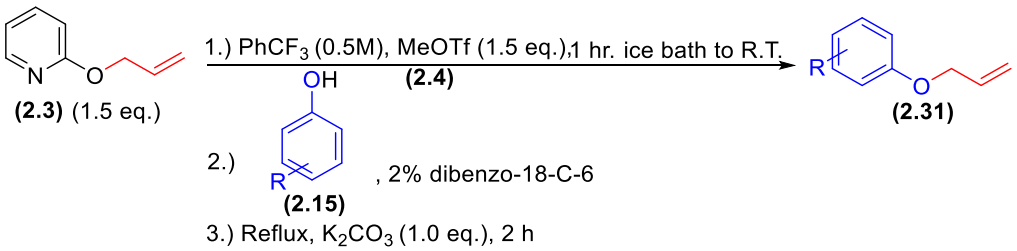


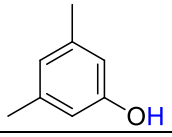
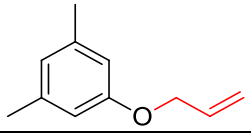
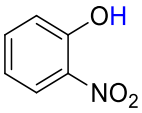
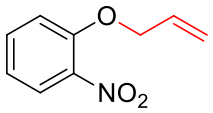
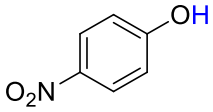
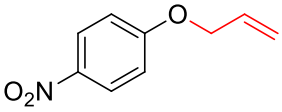
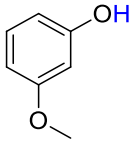
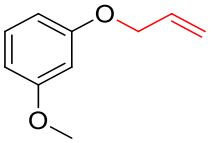
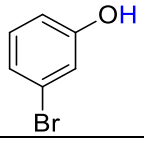
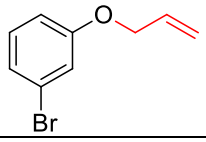
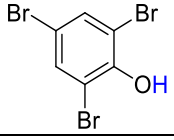
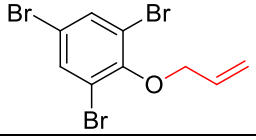
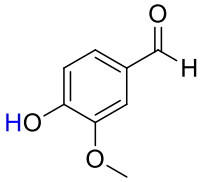
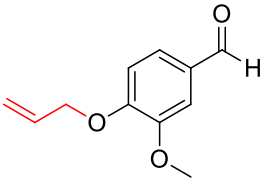
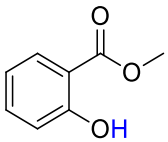
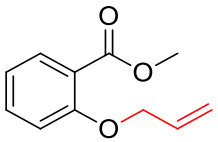
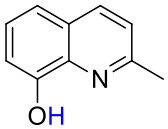
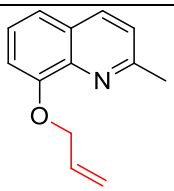
Scheme 2-10: Optimized Reaction for the Synthesis of Allyl Aryl Ethers *via* AMPT

After the method of synthesizing allyl ethers *via* phenols was optimized, other substrates were examined under optimized conditions **(Table 2-7)**. The original substrate examined, 3,5-dimethylphenol, has two electron donating methyl groups (entry **2.15a**). It was also beneficial to test *ortho*-nitrophenol and *para*-nitrophenol (entries **2.15b** and **2.15c**). They both have similar electronic affects, but differ in steric effects. The nitro groups act as an electron-withdrawing

group. However, the *ortho* nitro group causes more steric hindrance than its *para* nitro counterpart does. The corresponding product (entry **2.31d**) of 3-methoxyphenol (entry **2.15d**) proved to be the most difficult of the following substrates to isolate due to the byproducts being of similar polarity. The byproducts included similar allyl species, often in trace amounts. When a nonpolar allyl byproduct formed, it was sometimes difficult to isolate due to coelution. The corresponding products (entries **2.31e** and **2.31f**) of the nonpolar substrates such as 3-bromophenol (entry **2.15e**) and 2,4,6-tribromophenol (entry **2.15f**) were easily isolated because the byproducts formed were not similar to the product in terms of polarity. The corresponding products (entries **2.31g** and **2.31h**) of 4-Hydroxy-3-methoxybenzaldehyde and 2-(Methoxycarbonyl) phenol (entries **2.15g** and **2.15h**) are polar compounds and are easily isolated *via* flash chromatography. 8-hydroxyquinaldine (entry **2.15i**) was a heterocycle substrate examined, which showed high yields when synthesized to its corresponding product (entry **2.31i**). The conventional method of using allyl bromide for phenols would only yield about a 70% after 20 h, opposed to this new method of allylating phenols in 2 h or less for substantially higher yields.[10] The method of synthesizing allyl ethers was optimized and *via* oxypyridinium salts and a scope of substrates were successfully examined to show high product yields.

Table 2-7: Phenol Substrate Screening



Entry	Substrate	Entry	Allyl Ether	Yield
2.15a		**2.31a**		82%
2.15b		**2.31b**		95%
2.15c		**2.31c**		>99%
2.15d		**2.31d**		76%
2.15e		**2.31e**		97%
2.15f		**2.31f**		92%
2.15g		**2.31g**		97%
2.15h		**2.31h**		94%
2.15i		**2.31i**		99%

2.10 Conclusions

Overall, the optimization method for synthesizing allyl ethers *via* phenol substrates proved to be successful. The solubility issues of the insoluble base and insoluble salt were resolved mainly by utilizing a catalyst to solubilize the base, and increasing surface area of the reaction. Under optimized conditions for transferring allyl groups to phenols, alcohol reactions still seemed to resist high yield allyl transfers. This phenomenon could possibly be due to reactivity issues, as opposed to the solubility issues phenols originally endured. Conventional methods in literature for allyl etherification, such as using allyl bromides for phenols, takes a much longer amount of time for lower yields than our method.[10] Optimizing the allyl etherification methodology for phenols is not only a significant accomplishment, but also facilitates the possible methods of optimizing the transfer of allyl groups to alcohols efficiently.

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CHAPTER III: EXPERIMENTAL AND SPECTRA

General Methodology and Experimental Procedures

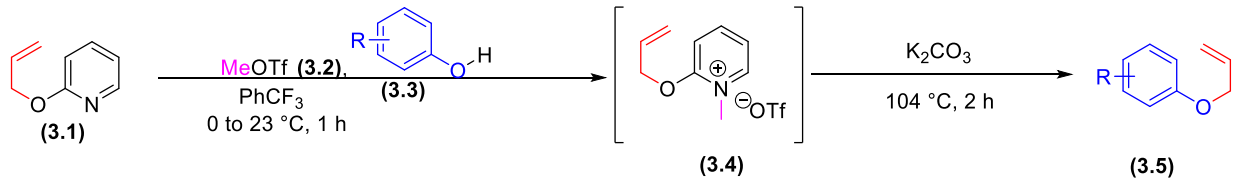


Table of Contents

General Techniques

Reactions

All chemicals originated from Sigma-Aldrich, including *α, α, α* – Trifluorotoluene and toluene, which were distilled, purged with argon, and stored over 4Å sieves.

During all experiments, flasks, syringes, stir bars, needles, NMR tubes, and other glassware were heated in an oven for 24 h and dried in a Bel-Art Scienceware Desiccator. 14/20 size glassware was mainly used. Flasks were heated on an IKA hot plate or OptiChem Digital Hotplate Stirrer, both with digital thermometers.

The reactions were performed in inert conditions using argon. Stir bars were used to mix the solutions efficiently. 25 mL round bottom flasks were used to hold the reactants for all optimized substrate screenings. During monitoring, *p*-anisaldehyde solution and occasionally permanganate solution was used to stain the Whatman UV 254 aluminum back silica plates *via* a UVP compact UV lamp.

Extraction

During extraction, all separated organic layers were dried *via* anhydrous sodium sulfate. All reactions had any remaining solvent separated *via* Buchi Rotavapor RII and a Buchi oil-free vacuum pump. Any remaining water or solvents were evaporated using a Welch 1400 DuoSeal Vacuum Pump.

Purification

During purifications, Dynamic Adsorbents Inc. Flash Grade Silica Gel was used in columns, and Chloroform-D with TMS was used to solubilize the contents of the flasks for NMR proton and carbon spectra. All samples were weighed using the Mettler Toledo scale. Reactions were purified using hexane and ethyl acetate eluents. Reactions were purified *via* flash

chromatography. All reactions were later stored in the Isotemp Fisher Scientific laboratory refrigerator.

General Instruments and Materials

Bel-Art Scienceware Desiccator

Chloroform-D with TMS

Dynamic Adsorbents Inc. Flash Grade Silica Gel

IKA hot plate and with a digital thermometer

Isotemp Fisher Scientific laboratory refrigerator

Kewaunee Scientific Corporation hoods

KNF Laboratories oil-free filtration pump

Mettler Toledo scale

OptiChem Digital Hotplate Stirrer

p-Anisaldehyde solution – (6 g Anisaldehyde, 250 mL Ethanol, 2.5 mL Concentrated H_2SO_4)

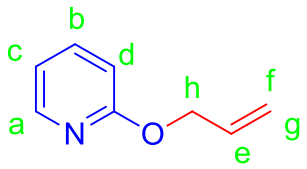
Permanganate solution – (1 g $KMnO_4$, 6.5 g K_2CO_3, 2 mL 5% NaOH, 100 mL Water)

Silicone oil

UVP compact UV lamp

Welch 1400 DuoSeal Vacuum Pump

Whatman UV 254 aluminum back silica plates



(3.1)

2-Allyloxypyridine – A single neck 500 mL round bottom flask used for the reactions. 85% KOH (22.0461 g, 393.0 mmol) was ground in a mortar and pestle. Sequentially, allyl alcohol (11.5 mL, 169.1 mmol), 2-Chloropyridine (10.5 mL, 111.1 mmol), 85% KOH (22.0461 g, 393.0 mmol), toluene (225 mL) were placed in the large flask. The reaction was allowed to stir *via* medium sized stir bar, and was allowed to heat at 111 °C under an argon atmosphere for 24 h. The reaction mixture was diluted using dichloromethane (75 mL), water (75 mL), and was followed with brine (75 mL). The organic portion was dried over anhydrous sodium sulfate. Any remaining solvent was filtered, and then removed *in vacuo*. The crude product was purified *via* column chromatography at a ratio of 19:1 hexane: ethyl acetate eluent to yield the product 2-Allyoxypyridine as a slightly yellow oil (14.6564 g, 108.43 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, J = 4.7 Hz, 1.8 Hz, 1Ha); 7.56 (ddd, J = 8.2 Hz, 7.0 Hz, 1.3 Hz, 1Hb); 6.86 (ddd, J = 7.3 Hz, 5.4 Hz, 1.1 Hz, 1H c); 6.76 (dt, J = 8.4, 1.0 Hz, 1Hd); 6.09 (ddt, J = 17.2 Hz, 10.9 Hz, 5.5 Hz, 1He); 5.41 (dq, J = 17.1 Hz, 1.8 Hz, 1Hf); 5.25 (dq, J = 10.6 Hz, 1.1 Hz, 1Hg); 4.83 (dt, 5.5, 1.1 Hz, 2Hh) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 146.9, 138.7, 133.7, 117.4, 116.9, 111.3, 66.5 ppm. FTIR (ATR cm^{-1}): 3081, 3017, 2936 (C-H str); 1649 (C=C str); 1595, 1570, 1473 aromatics.

General Procedure for the Formation of Allyl Ethers

A 25 mL round bottom flask was coupled with a stir bar, a rubber septum, and an argon needle. The flask was filled with 2-allyloxypyridine (1.5 equiv.) and anhydrous $PhCF_3$(~ 0.8 mL). The reaction was allowed to stir in an ice bath at 0 °C, while MeOTf (1.5) was added dropwise over the duration of 10-15 min. The reaction was allowed to stir for the remaining 45 minutes in the ice bath, and then the flask was allowed to warm up to room temperature. The substrate (1.0) was allowed to dissolve in catalyst (1%) with the solvent $PhCF_3$ (~0.3 mL) *via* disposable vial. The solution was then transferred to the 25 mL reaction flask *via* disposable syringe followed by washing 0.15 mL of solvent in the vial. If the substrate was unable to be solubilized using $PhCF_3$, then the substrate was directly added to the flask *via* weighing paper, while $PhCF_3$ was then directly added to the 25 mL flask *via* syringe. The reaction mixture was then heated in an oil bath to 104 °C. Then K_2CO_3 (1.0) was added directly to the flask *via* weighing paper, and a curved metal spatula was used to ensure all K_2CO_3 was in the reaction mixture and not fixed to the sides of the reaction flask. The reaction mixture was then allowed to reflux under argon conditions for 2 h. Then the reaction mixture was diluted with ethyl acetate (10-15 mL), water (3 x 10-15 mL), and then washed with brine (10-15 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered, and then solvent was removed *in vacuo*. The product was then purified *via* flash chromatography to yield the desired allyl ether product **(3.5)**.

Obtaining Spectra and Analytical Data

^{1}H-NMR – All ^{1}H NMR spectra were collected *via* JEOL 400 MHz Multinuclear FT-NMR spectrometer.

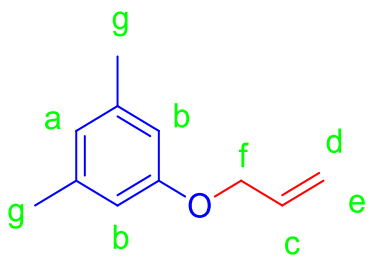
^{13}C-NMR – All ^{13}C NMR spectra were collected *via* JEOL 400 MHz spectrometer

IR – All infrared spectrometer spectra were collected *via* PerkinElmer Spectrum100 TF-IR Spectrometer.

Reagents

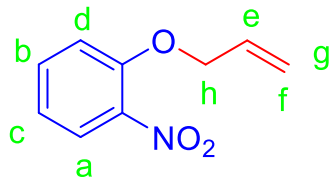
Allyl alcohol – ≥99%, Sigma Aldrich
2-Chloropyridine – ≥ 99%, Sigma Aldrich
Potassium Hydroxide – ≥ 85%, Sigma Aldrich
Dibenzo-18-Crown-6 – 99%, Sigma Aldrich
MeOTf – ≥99%, Sigma Aldrich
3,5-Dimethylphenol – ≥ 99%, Aldrich
Para-nirophenol – ≥ 99%, Aldrich
Ortho-nitrophenol – ≥ 99%, Aldrich
4-Methoxyphenol – ≥ 99%, Aldrich
3-Bromophenol – ≥ 99%, Aldrich
2,4,6-Tribromophenol – ≥ 99%, Aldrich
4-Hydroxy-3-methoxybenzaldehyde – ≥ 99%, Aldrich
2-(Methoxycarbonyl) phenol – ≥ 99%, Aldrich
8-hydroxyquinaldine – ≥ 98%, Aldrich

The significant precursor reactants included utilizing allyl alcohol and 2-chloropyridine to synthesize 2-allyloxypyridine. MeOTf was used to convert 2-allyloxypyridine into a reactive salt for *in-situ* allyl etherification reactions.



(3.5a)

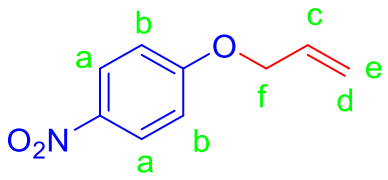
Allyloxy-3,5-dimethylbenzene. 3,5-dimethylphenol (0.0567 g, 0.4641 mmol) was subjected to the general procedure (page 53). The crude product was purified *via* flash column chromatography at a ratio of 99:1 hexane: ethyl acetate eluent to yield Allyloxy-3,5-dimethylbenzene **(3.5a)** as a colorless oil (0.062 g, 0.3822 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 1Ha); 6.54 (s, 2Hb); 6.05 (ddt, J = 17.1 Hz, 10.6 Hz, 5.9 Hz, 1Hc); 5.40 (dq, J = 17.2 Hz, 1.4 Hz, 1Hd); 5.27 (dq, J = 10.6 Hz, 1.5 Hz, 1He); 4.50 (dt, J = 5.5, 1.8 Hz, 2Hf); 2.27 (s, 6Hg) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 139.2, 133.6, 122.7, 117.5, 112.6, 68.7, 21.5 ppm. FTIR (ATR cm^{-1}): 3014, 2920, 2857 (C-H str); 1594, 1457, 1321 aromatics.



(3.5b)

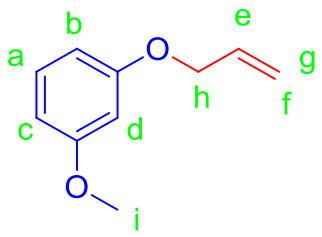
Allyloxy-2-nitrobenzene. *Ortho*-nitrophenol (0.0581 g, 0.4205 mmol) was subjected to the general procedure (page 53). The crude product was purified *via* flash column chromatography at a ratio of 7:1 hexane: ethyl acetate eluent to yield Allyloxy-2-nitrobenzene **(3.5b)** as a yellow oil (0.071 g, 0.3963 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 8.4, 1.8 Hz, 1H a); 7.50 (ddd, J = 9.2, 7.7, 1.8 Hz. 1Hb); 7.00-7.07 (m, 2H c-d); 6.03 (ddt J = 17.2, 10.6 Hz, 5.1 Hz, 1He); 5.48 (dq, J = 17.2, 1.2 Hz, 1Hf); 5.33 (dq, J = 10.6, 1.5Hz, 1Hg); 4.68 (dt, J = 5.2 Hz, 2Hh) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 140.2, 134.0, 131.8, 125.7, 120.6, 118.2, 115.0, 70.1 ppm. FTIR (ATR cm^{-1}): 3081, 2930, 2868 (C-H str); 1520, 1348 (N-O str); 1606, 1583 aromatics.



(3.5c)

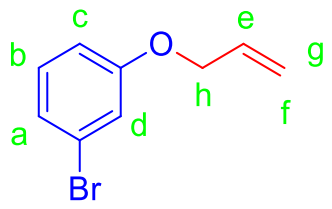
Allyloxy-4-nitrobenzene. *Para*-nitrophenol (0.0583 g, 0.4191 mmol) was subjected to the general procedure (page 53). The crude product was purified *via* flash column chromatography at a ratio of 9:1 hexane: ethyl acetate eluent to yield Allyloxy-4-nitrobenzene **(3.5c)** as a yellow oil (.0746 g, 0.4164 mmol, >99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dt, J = 13.9, 4.4 Hz, 2Ha); 7.00 (dt, J = 13.9 Hz, 4.4 Hz, 2Hb); 6.04 (ddt, J = 17.4 Hz, 10.2 Hz, 5.5 Hz, 1Hc); 5.43 (dq, J = 17.2 Hz, 1.4 Hz, 1Hd); 5.36 (dq, J = 10.2 Hz, 1.5 Hz, 1He); 4.63 (dt, J = 6.7, 1.8 Hz, 2Hf) ppm.^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 141.7, 132.0, 126.0, 118.76, 118.77, 114.78, 114.79, 69.5 ppm. FTIR (ATR cm^{-1}): 3087, 2930 (C-H str); 1494, 1508 (N-O str); 1590 aromatic.



(3.5d)

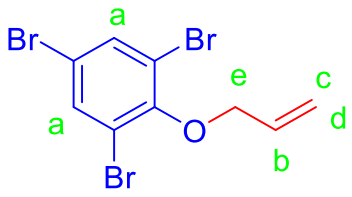
Allyloxy-3-methoxyphenol. 3-methoxyphenol (.0580 g, .4592 mmol) was subjected to the general procedure (page 53). The crude product was purified *via* column chromatography at a ratio of 149:1 hexane: ethyl acetate eluent to yield Allyloxy-3-methoxyphenol **(3.5d)** as colorless oil (0.057 g, 0.3471 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, J = 8.1 Hz, 1Ha); 6.50-6.54 (m, 3Hb-d); 6.06 (ddt, J = 17.3, 10.6, 5.5, 1He); 5.42 (dq, J = 17.1, 1.5 Hz, 1Hf); 5.29 (dq, J =

10.6, 1.5 Hz, 1Hg); 4.52 (dt, *J* = 5.2, 2.2 Hz, 2Hh); 3.78 (s, 3Hi) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 160.0, 133.4, 130.1, 117.8, 107.0, 106.5, 101.3, 69.0, 55.3 ppm. FTIR (ATR cm^{-1}): *v* 2924 (C-H str); 1147 (C-O-C str); 1592, 1491 aromatics.



(3.5e)

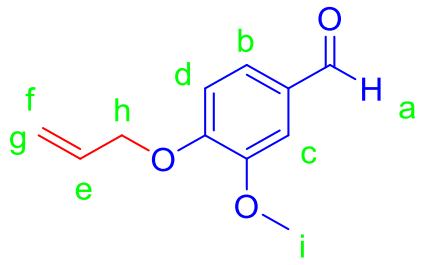
Allyloxy-3-bromobenzene. 3-bromophenol (0.0608 g, 0.3514 mmol) was subjected to the general procedure (page 53). The crude product was purified *via* flash column chromatography at a ratio of 149:1 hexane: ethyl acetate eluent to yield Allyloxy-3-bromobenzene **(3.5e)** as a colorless oil (0.073 g, 0.3426 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (td, *J* = 5.9, 2.2 Hz, 1Ha); 7.06-7.09 (m, 2Hb-c); 6.85-6.86 (m, 1Hd); 6.03 (ddt, *J* = 17.2 Hz, 10.6 Hz, 5.5 Hz, 1He); 5.43 (dq, *J* = 17.2 Hz, 1.5 Hz, 1Hf); 5.30 (dq, *J* = 10.6 Hz, 1.4 Hz, 1Hg); 4.51 (dt, *J* = 5.1, 1.4 Hz, 2Hh) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 132.8, 130.6, 124.0, 122.8, 118.12, 188.06, 113.9, 69.1. FTIR (ATR cm^{-1}): 3076, 2913, 2863 (C-H str); 678 (C-Br str); 1572, 1589 aromatics.



(3.5f)

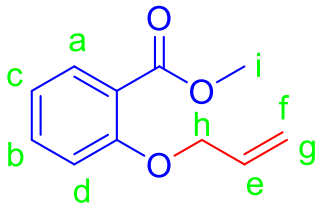
Allyl- 2,4,6-tribromophenyl ether. 2,4,6-tribromophenol (0.0670 g, 0.2025 mmol) was subjected to the general procedure (page 53). The crude product was purified *via* flash column chromatography at a ratio of 149:1 hexane: ethyl acetate eluent to yield Allyl-2,4,6-tribromophenylether **(3.5f)** as a white crystalline solid (0.069 g, 0.1861 mmol, 92%). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.65 (s, 2Ha); 6.15 (ddt, J = 17.3 Hz, 10.1 Hz, 5.5 Hz, 1Hb); 5.45 (dq, J = 17.1 Hz, 1.5 Hz, 1Hc); 5.32 (dq, J = 10.4 Hz, 1.4 Hz, 1Hd); 4.52 (dt, J = 8.0, 1.5 Hz, 2He) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 135.4, 135.1, 132.7, 119.3, 119.2, 119.1, 117.5, 74.3 ppm. FTIR (ATR cm^{-1}): 2920 (C-H str); 678, 735 (C-Br str); 1537 aromatic.



(3.5g)

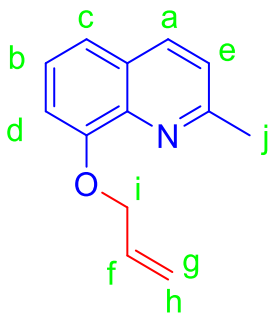
4-(Allyloxy)-3-methoxybenzaldehyde. 4-Hydroxy-3-methoxybenzaldehyde (0.0640g, 0.3902 mmol,) was subjected to the general procedure (page 53). The crude product was purified *via* flash column chromatography at a ratio of 3:1 hexane: ethyl acetate eluent to yield 4-(Allyloxy)-3-methoxybenzaldehyde **(3.5g)** as slightly yellow oil (0.073g, 0.3800 mmol, 97%). ^1H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1Ha); 7.41-7.43 (m, 2Hb-c); 6.97 (d, J = 8.8 Hz, 1Hd); 6.08 (ddt, J = 17.2 Hz, 10.6 Hz, 5.5 Hz, 1He); 5.43 (dq, J = 17.2 Hz, 1.1 Hz, 1Hf); 5.43 (dq, J = 10.6 Hz, 1.1 Hz, 1Hg); 4.70 (dt, J = 5.1, 1.5 Hz, 2Hh); 3.93 (s, 3Hi) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 153.6, 150.0, 132.3, 130.3, 126.7, 118.9, 112.0, 109.4, 69.9 ppm. FTIR (ATR cm^{-1}): 3076, 2936, 2834 (C-H str); 1679 (C=O str); 1584, 1506 aromatics.



(3.5h)

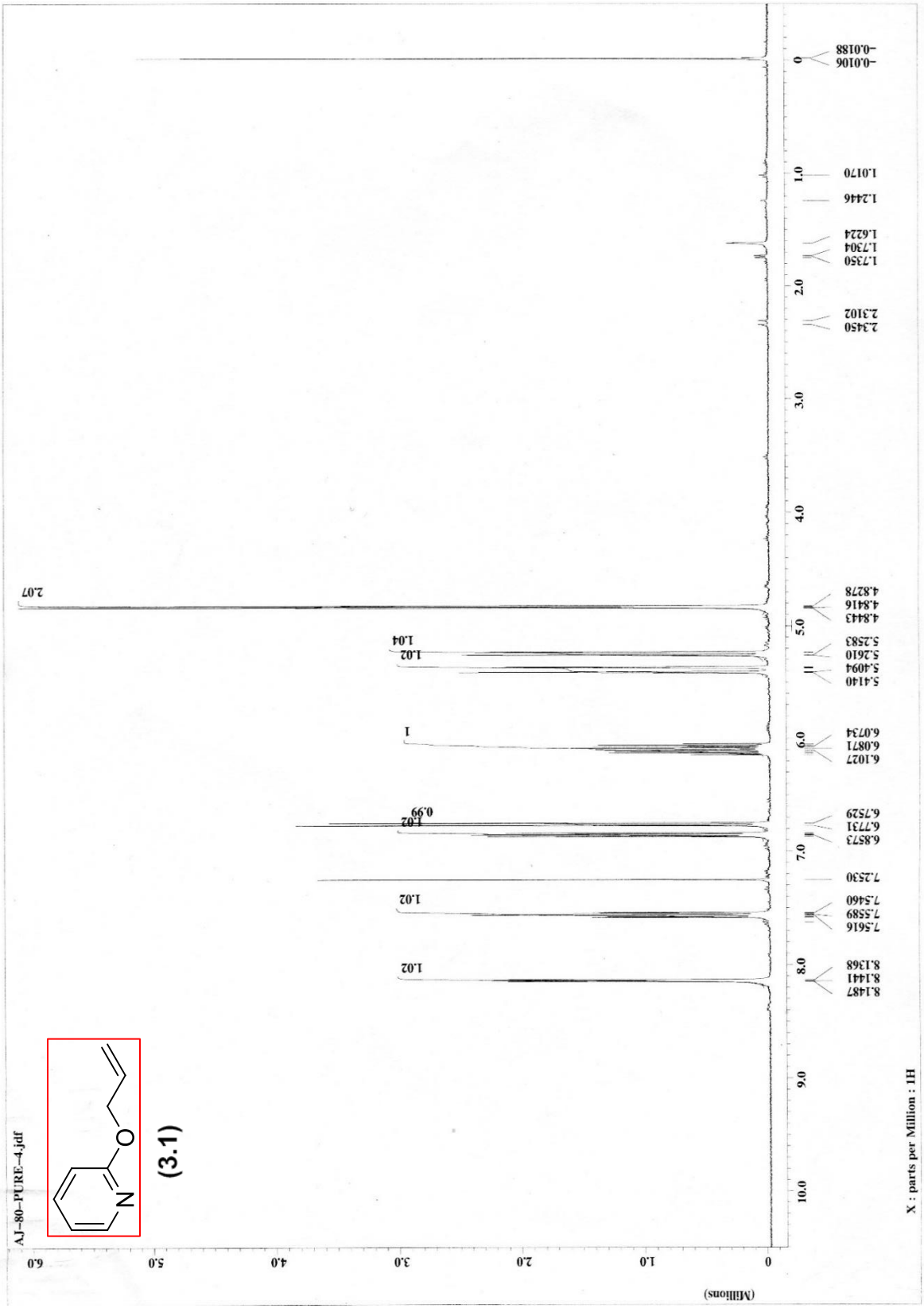
Methyl-2-(allyloxy) benzoate. 2-(Methoxycarbonyl) phenol (0.0660 g, 0.3943 mmol) was subjected to the general procedure (page 53). The crude product was purified *via* flash column

chromatography at a ratio of 19:1 hexane: ethyl acetate eluent to yield methyl-2-(allyloxy) benzoate **(3.5h)** as a colorless oil (0.071 g, 0.3798 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 7.7, 1.8 Hz, 1Ha); 7.43 (ddd, J = 8.4, 7.4, 1.8 Hz, 1Hb); 6.94-7.00 (m, 2Hc-d); 6.06 (ddt, J = 17.1, 9.9, 4.8 Hz, 1He); 5.51 (dq, J = 17.2, 1.8 Hz, 1Hf); 5.29 (dq, J = 10.6, 1.4 Hz, 1Hg); 4.62 (dt, J = 4.8, 1.8 Hz, 2Hh); 3.89 (s, 3Hi) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 158.2, 133.4, 132.8, 131.8, 120.7, 120.5, 117.5, 113.7, 69.5, 52.0 ppm. FTIR (ATR cm^{-1}): 2951 (C-H str); 1725 (C=O str); 1600, 1490 aromatics.



(3.5i)

2-Methyl-8-(2-propen-1-yloxy) quinoline. 8-hydroxyquinaldine (0.0599 g, 0.3769 mmol) was subjected to the general procedure (page 53). The crude product was purified *via* flash column chromatography at a ratio of 4:1 hexane: ethyl acetate eluent to yield 2-Methyl-8-(2-propen-1-yloxy) quinoline **(3.5i)** as a yellowish-orange oil (0.0746g, 0.3731 mmol, 99%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 8.4, 1.1 Hz, 1Ha); 7.25-7.37 (m, 3Hb-d); 7.04 (dd, J = 6.6, 2.6 Hz, 1He); 6.21 (ddt, J = 17.4, 10.6, 5.1 Hz, 1Hf); 5.47 (dq, J = 17.2, 1.4 Hz, 1Hg); 5.32 (dq, J = 10.6, 1.5 Hz, 1Hh); 4.88 (dt, J = 5.1, 1.4 Hz, 2Hi); 2.79 (s, 3Hj) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 153.9, 140.0, 136.1, 133.6, 127.8, 125.6, 122.6, 119.7, 118.0, 109.7, 70.0, 25.9 ppm. FTIR (ATR cm^{-1}): 3052, 2920, 2863 (C-H str); 1603 (C=N str); 1563, 1503 aromatics.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6.7529
6.1027
6.0871
6.0734
5.4140
5.4094
5.2610
5.2583
4.8443
4.8416
4.8278
2.3450
2.3102
1.7350
1.7304
1.6224
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1.02
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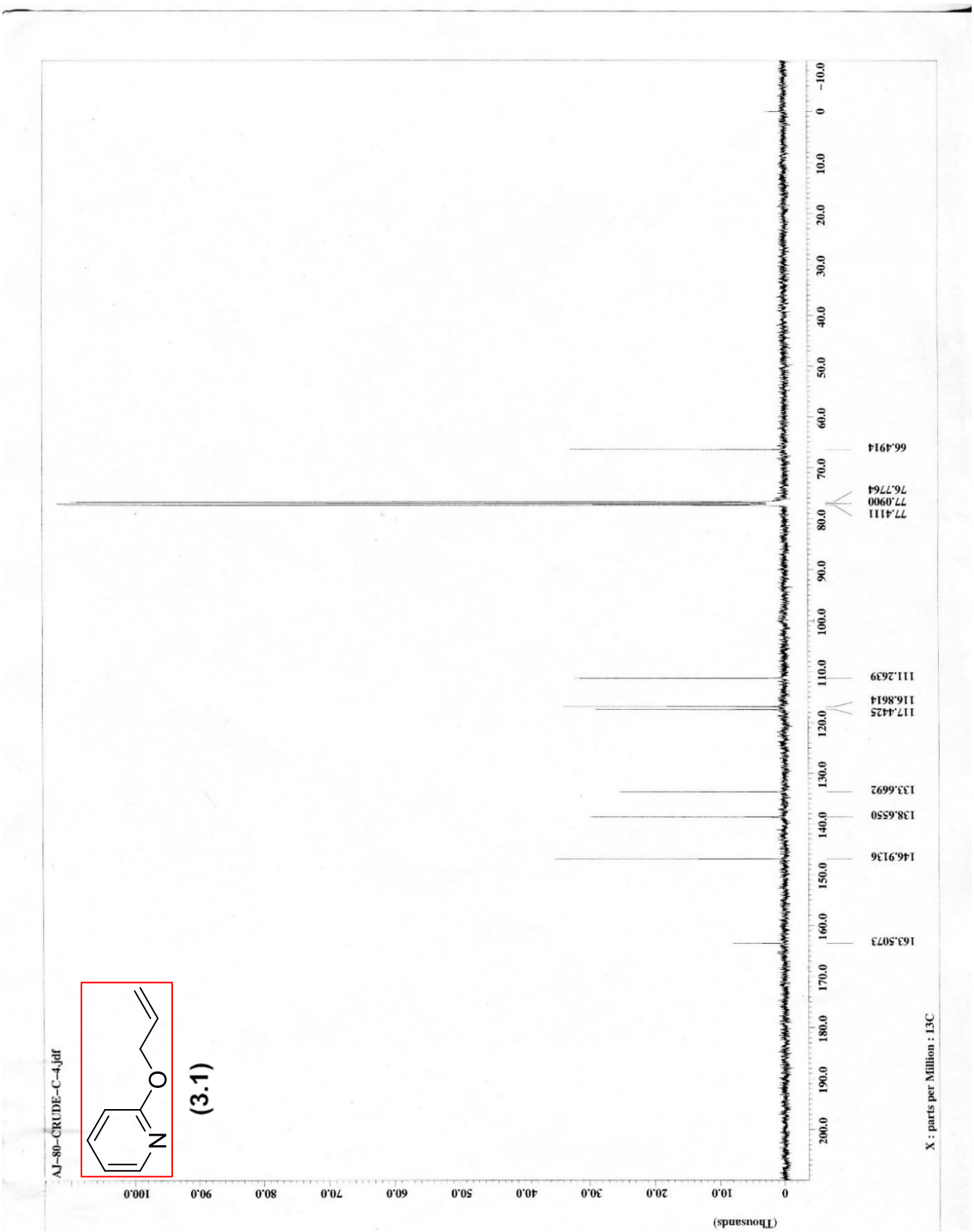
1.02
1.02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(Thousands)
X : parts per Million : 13C
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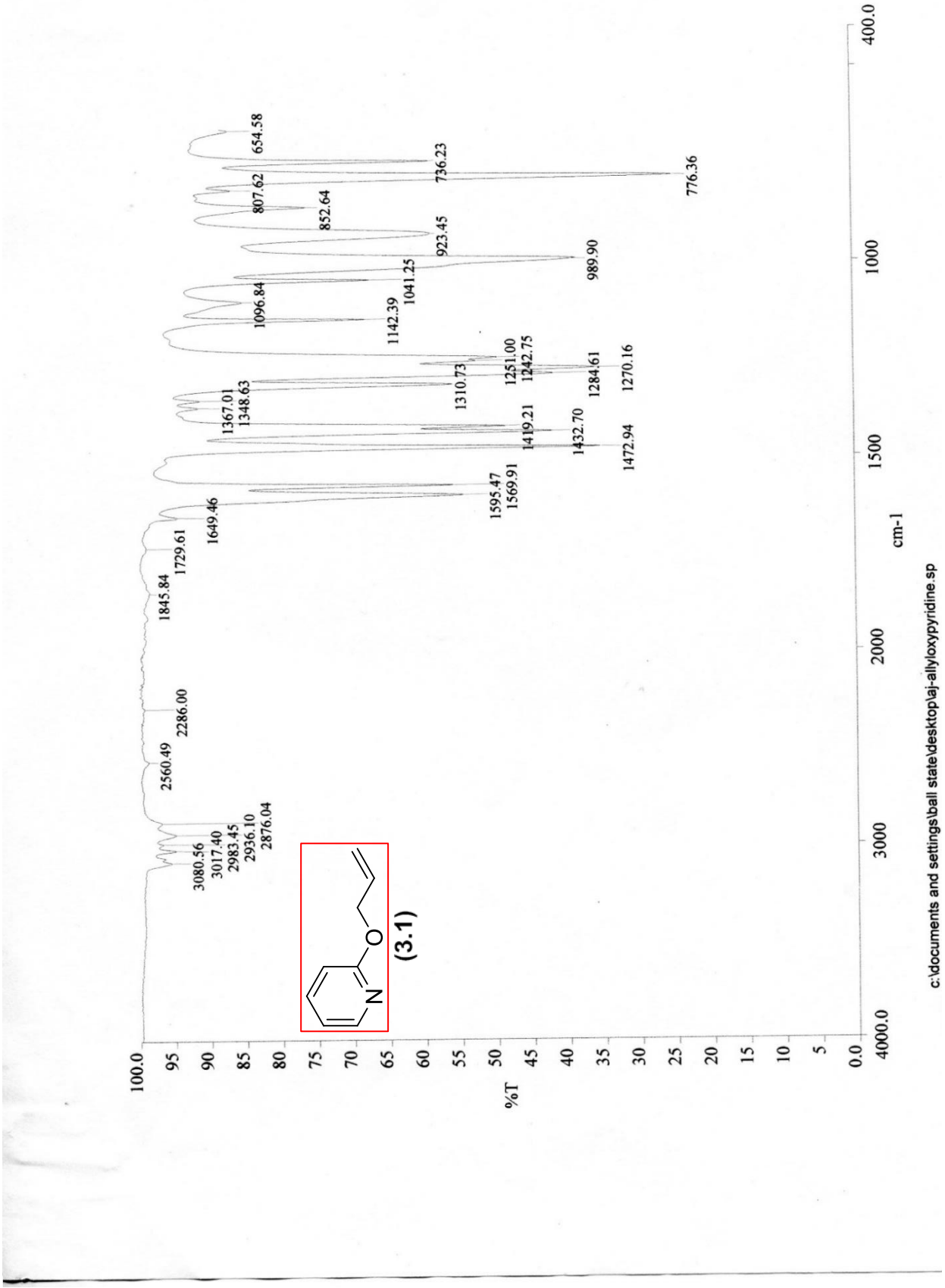
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1000
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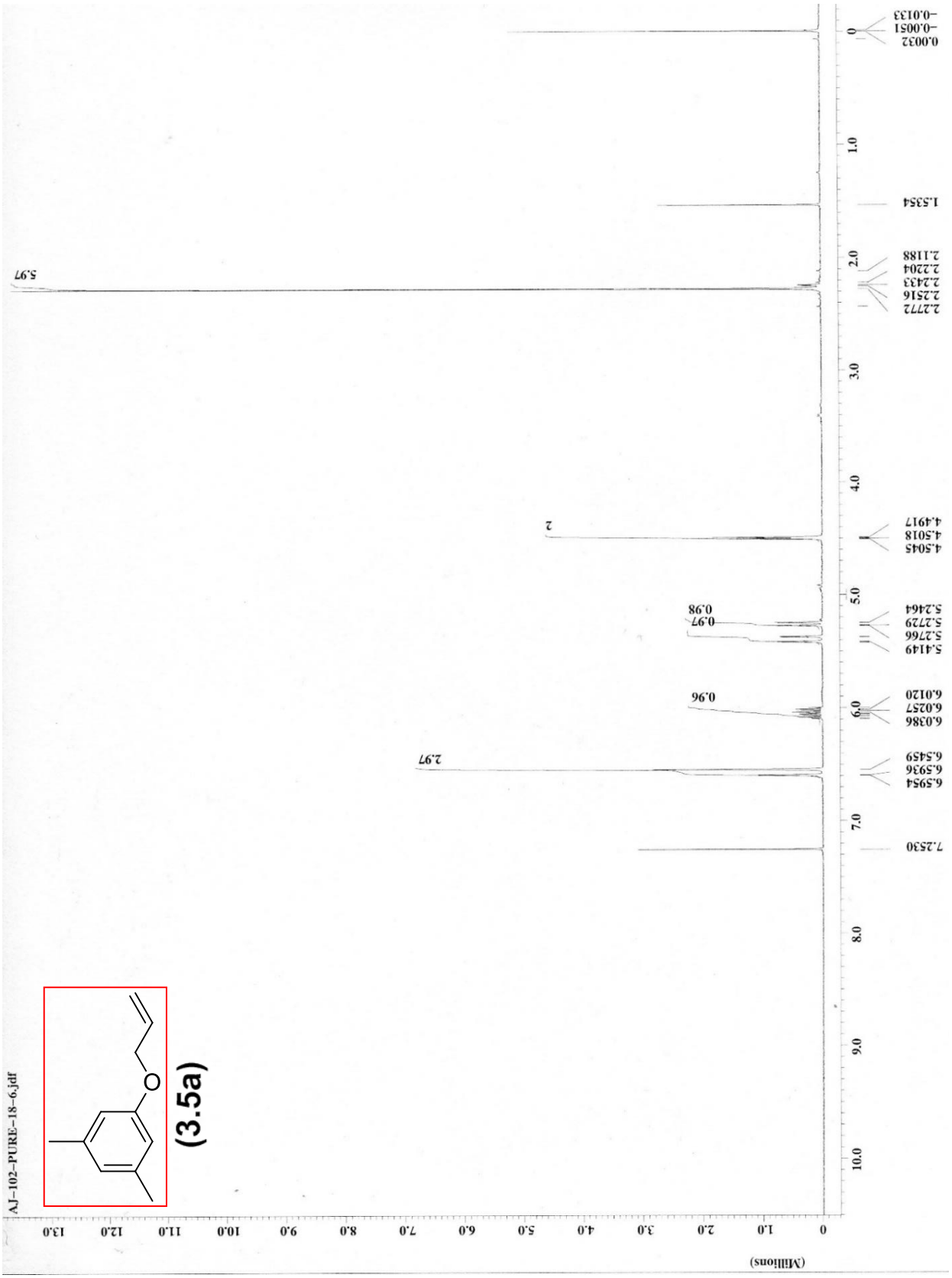
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5.2766
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4.5045
4.5018
4.4917
2.2772
2.2516
2.2433
2.2204
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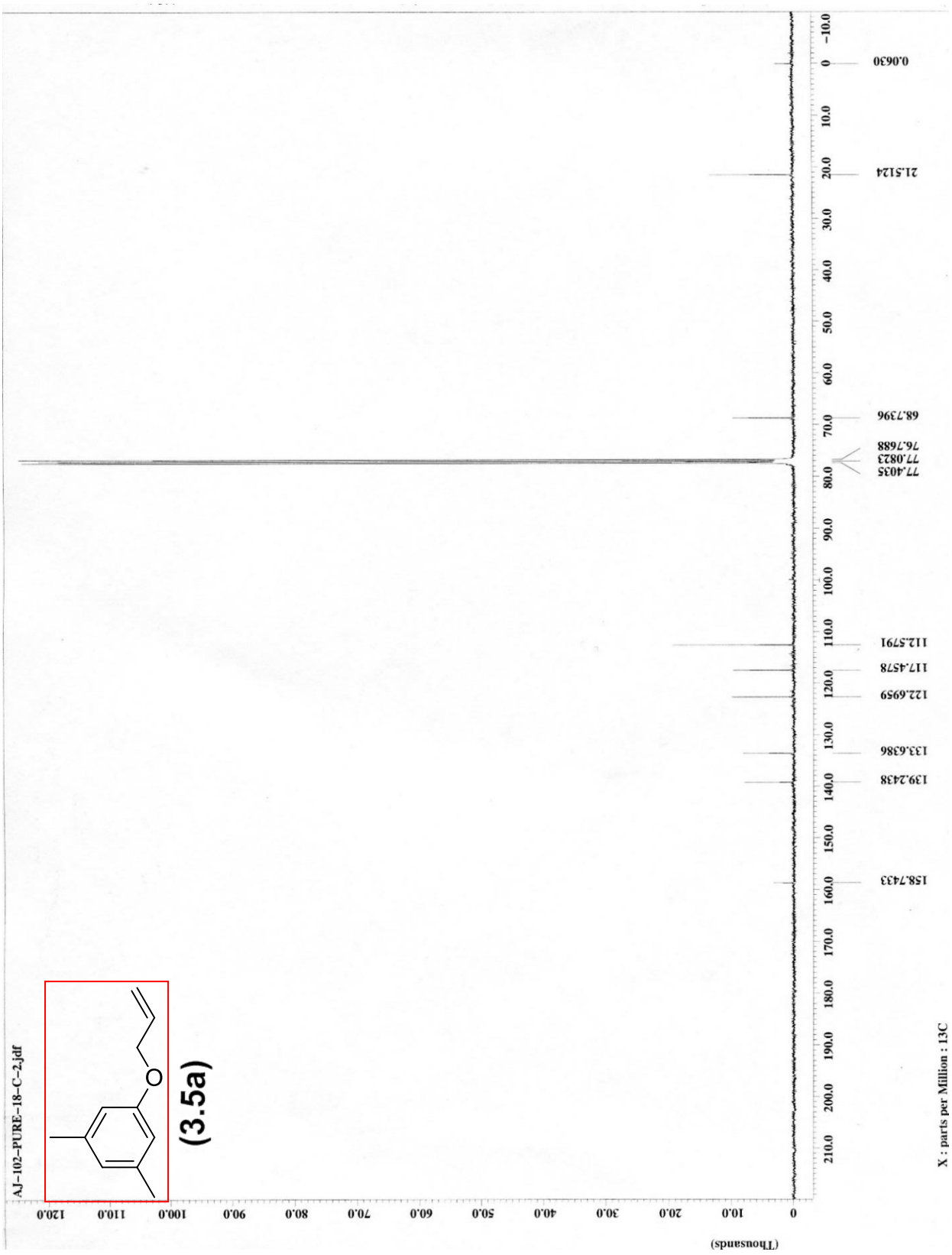
2.97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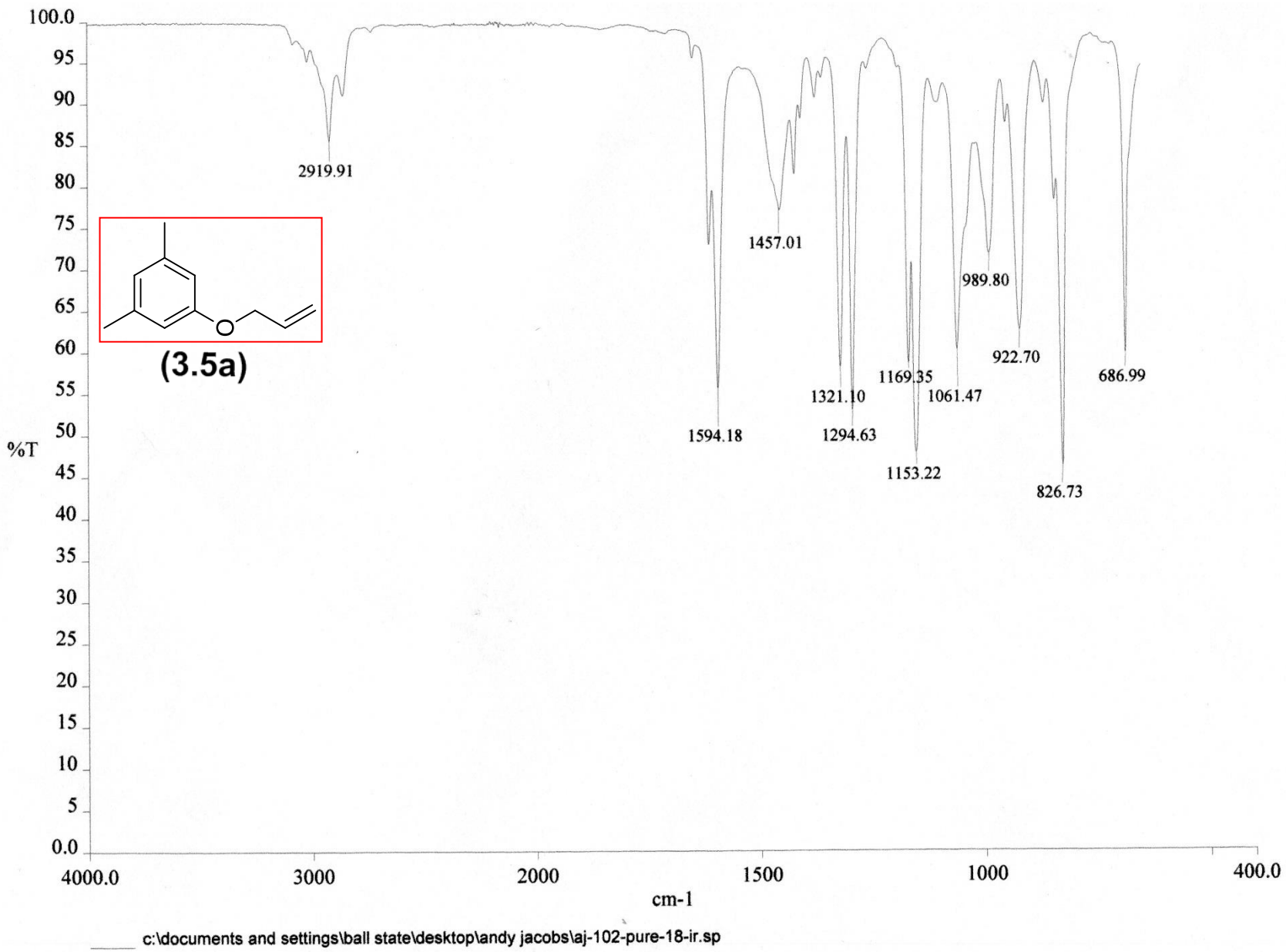
158.7433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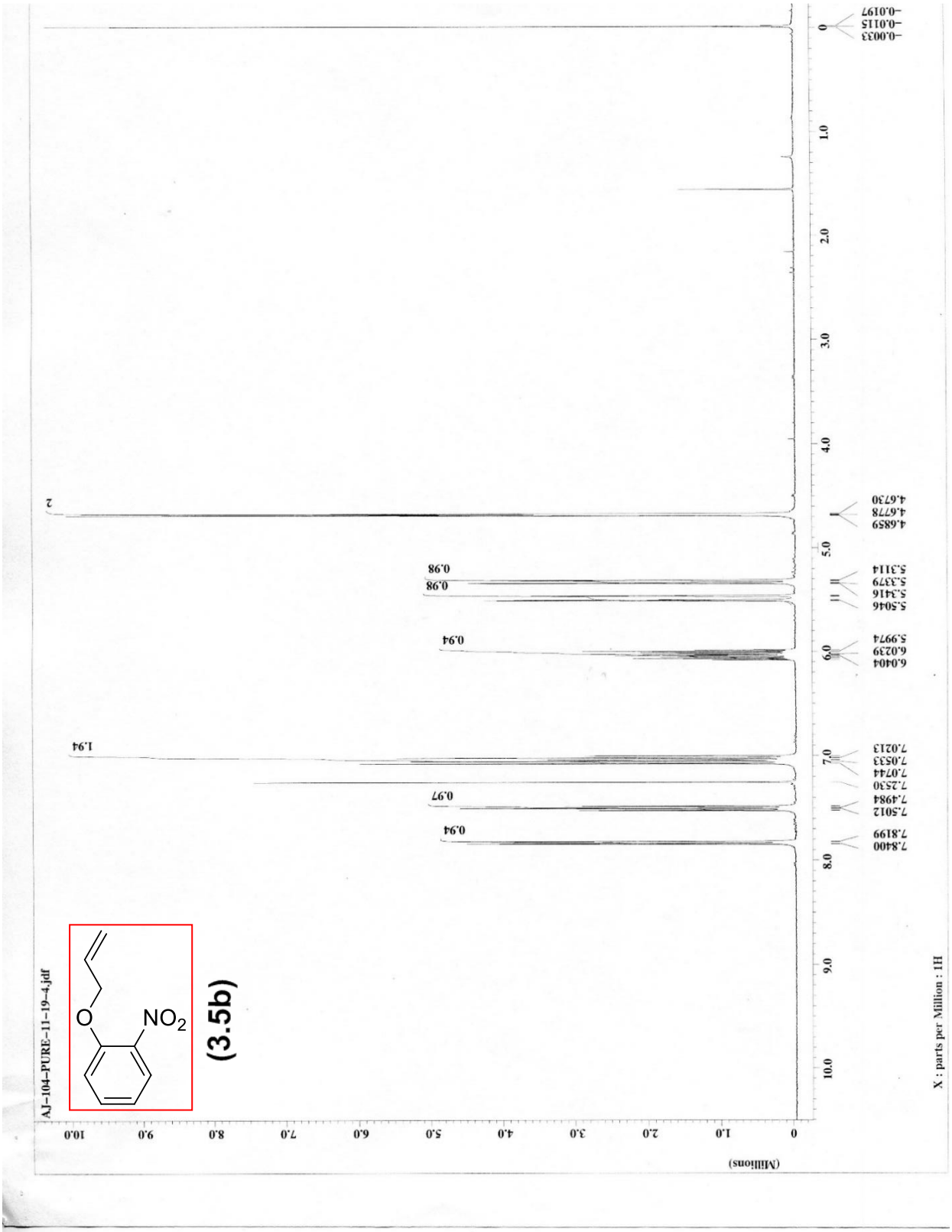
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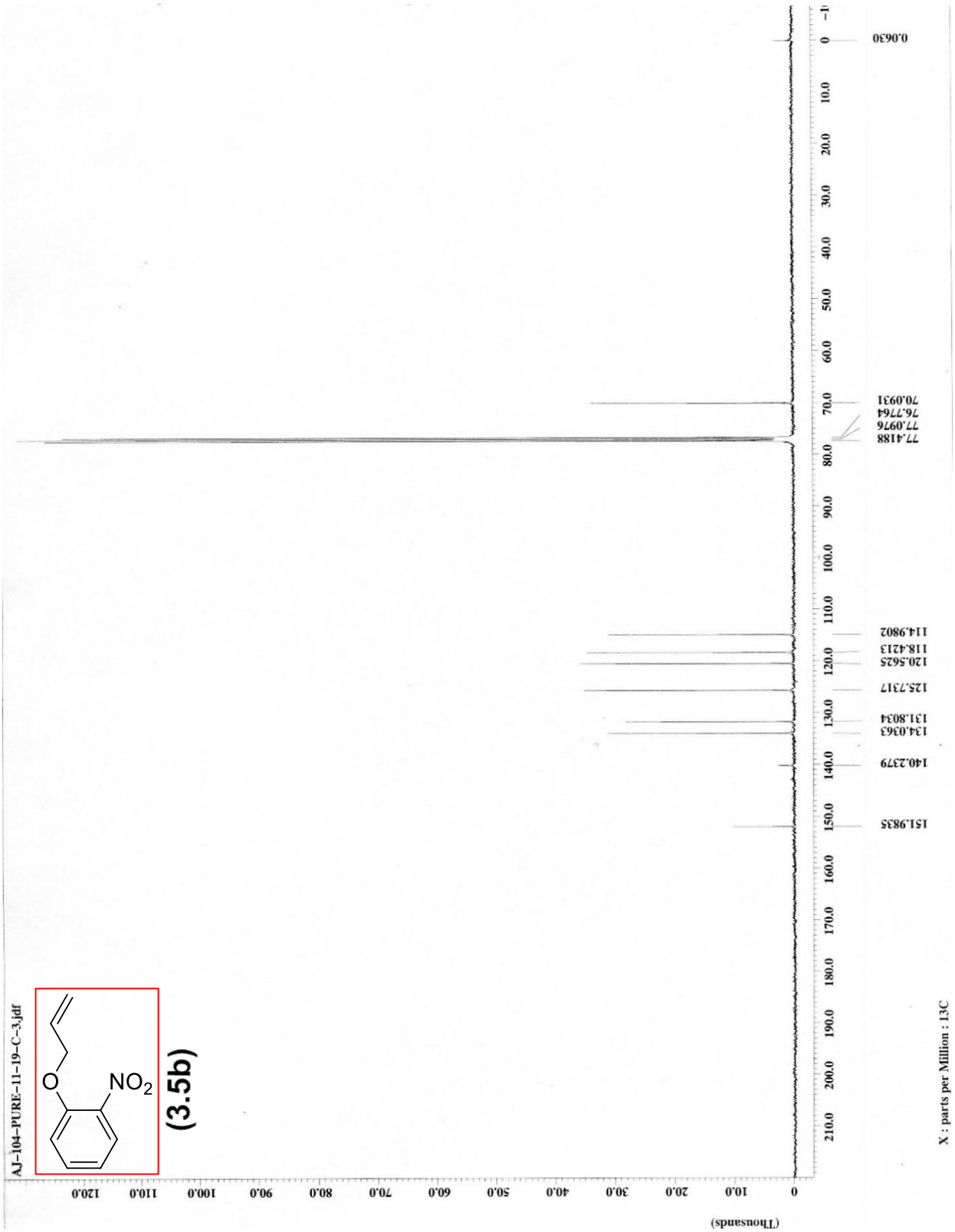
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NO2
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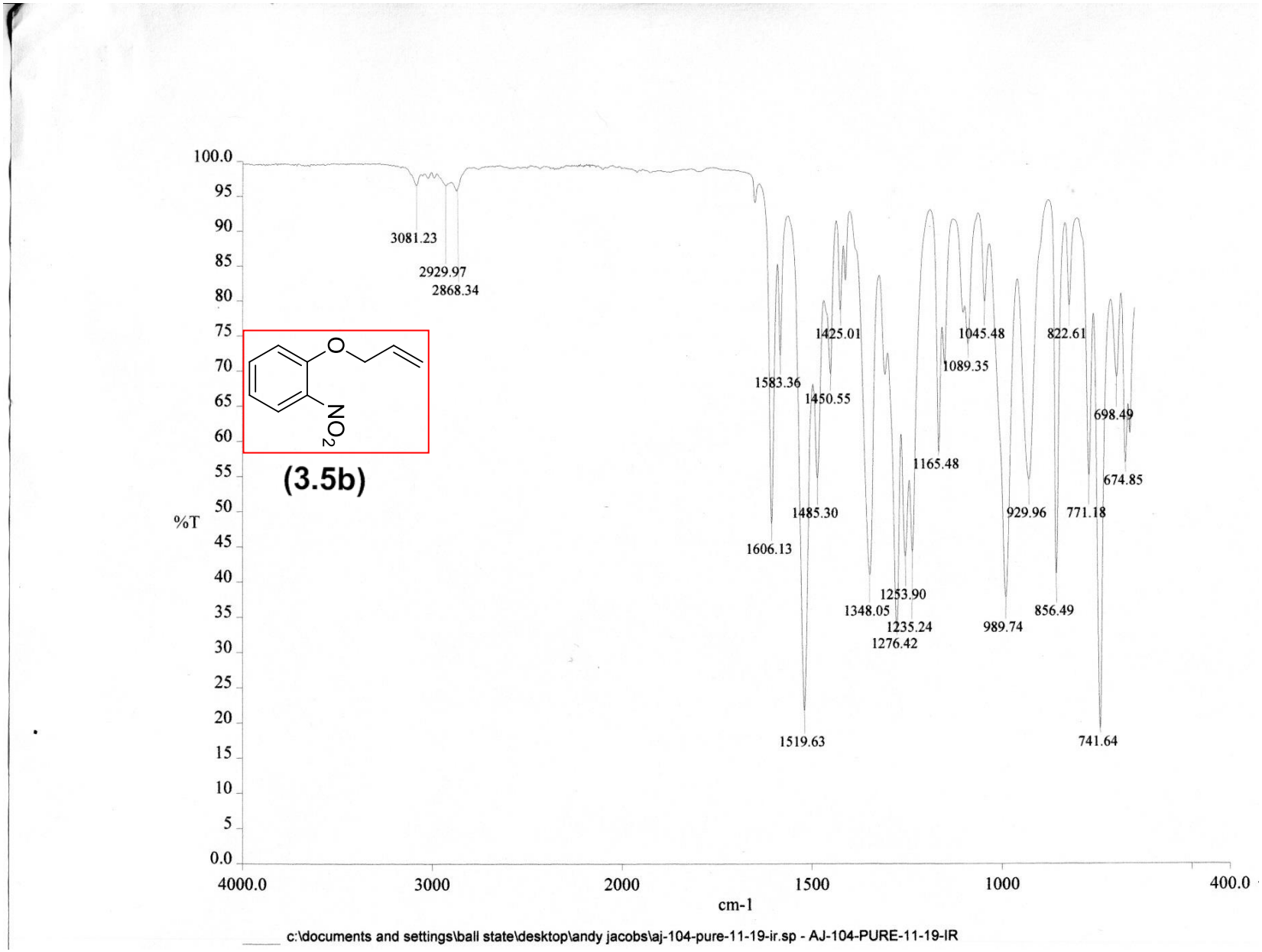
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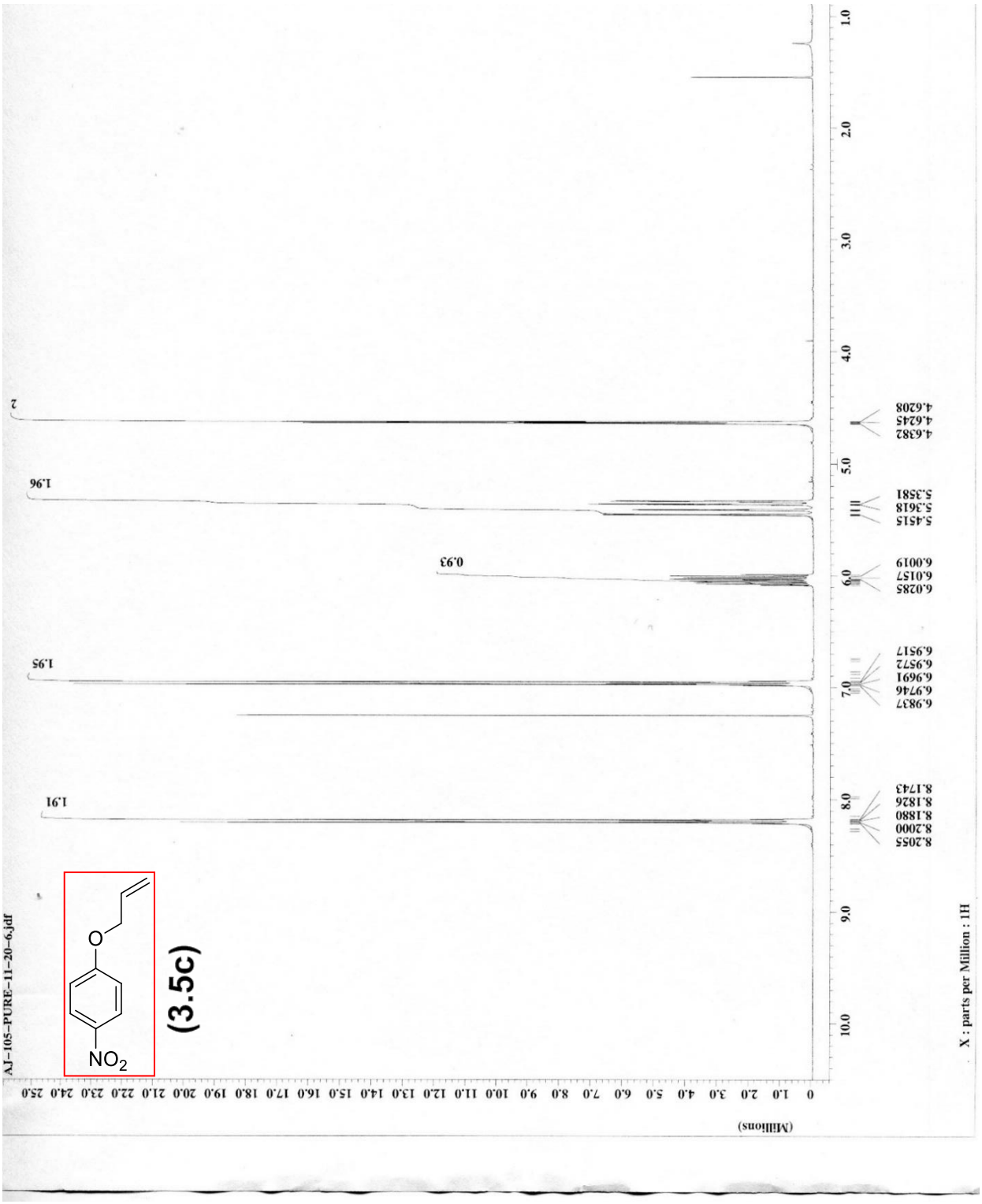
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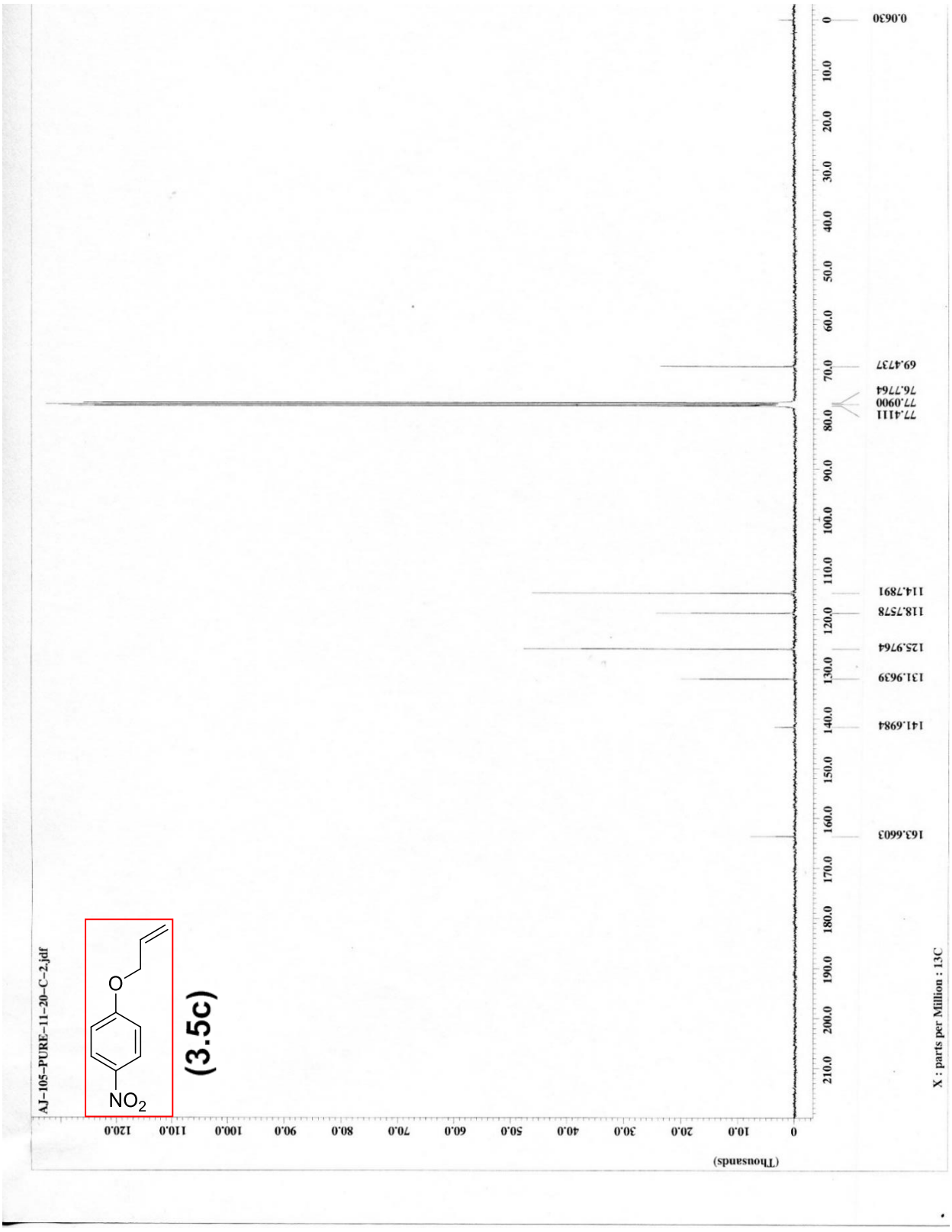
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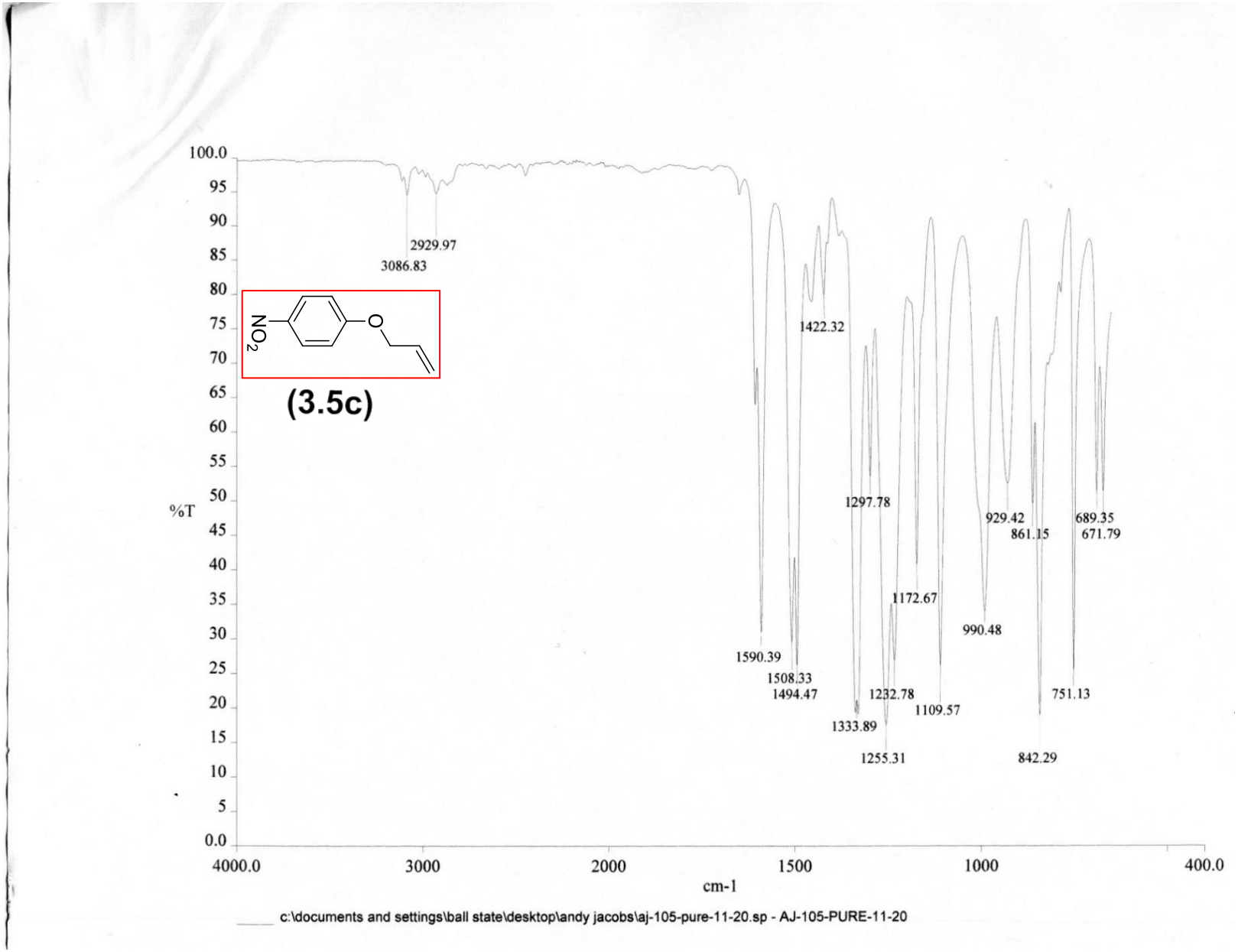
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1109.57
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1333.89
1255.31
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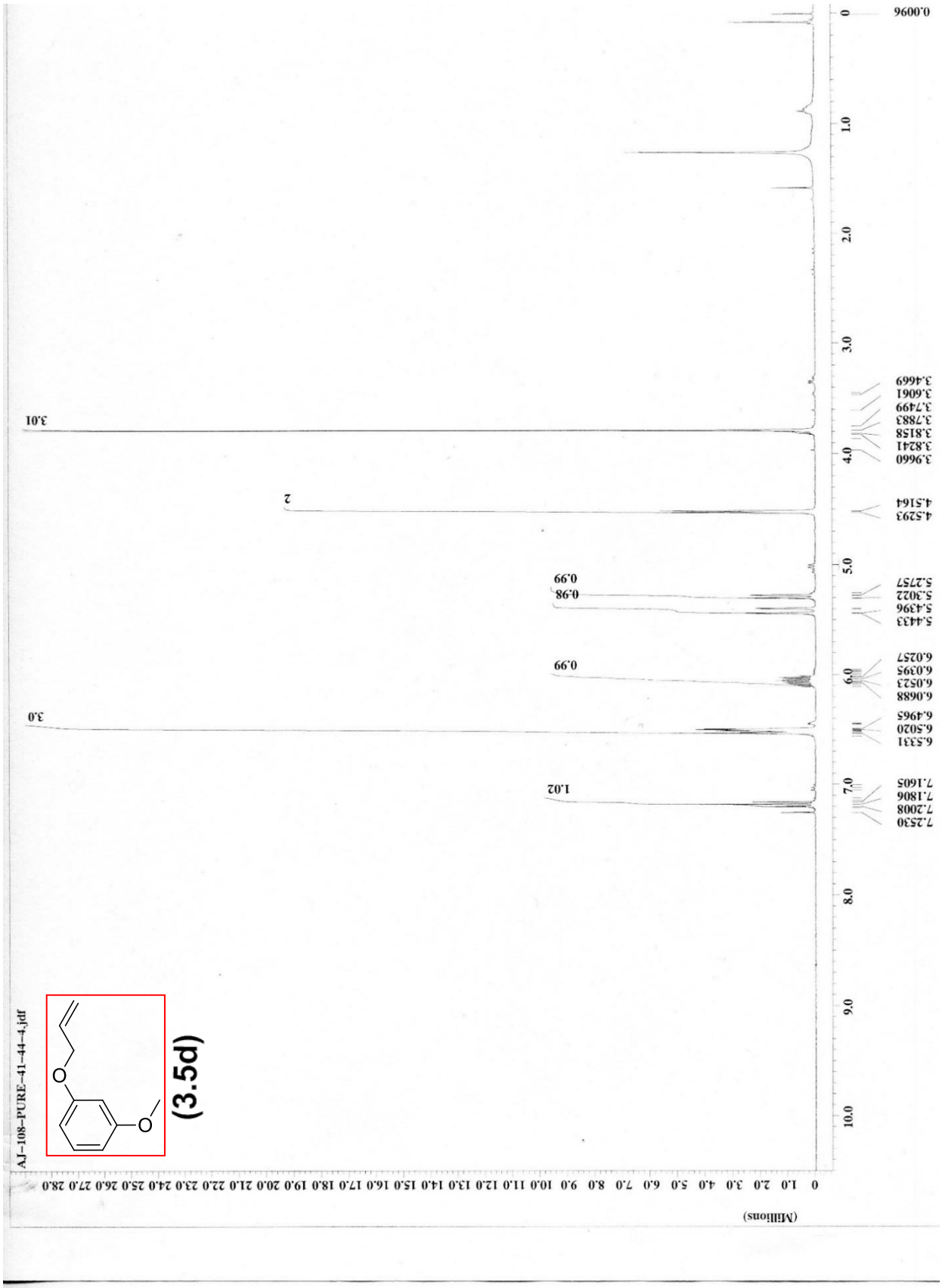
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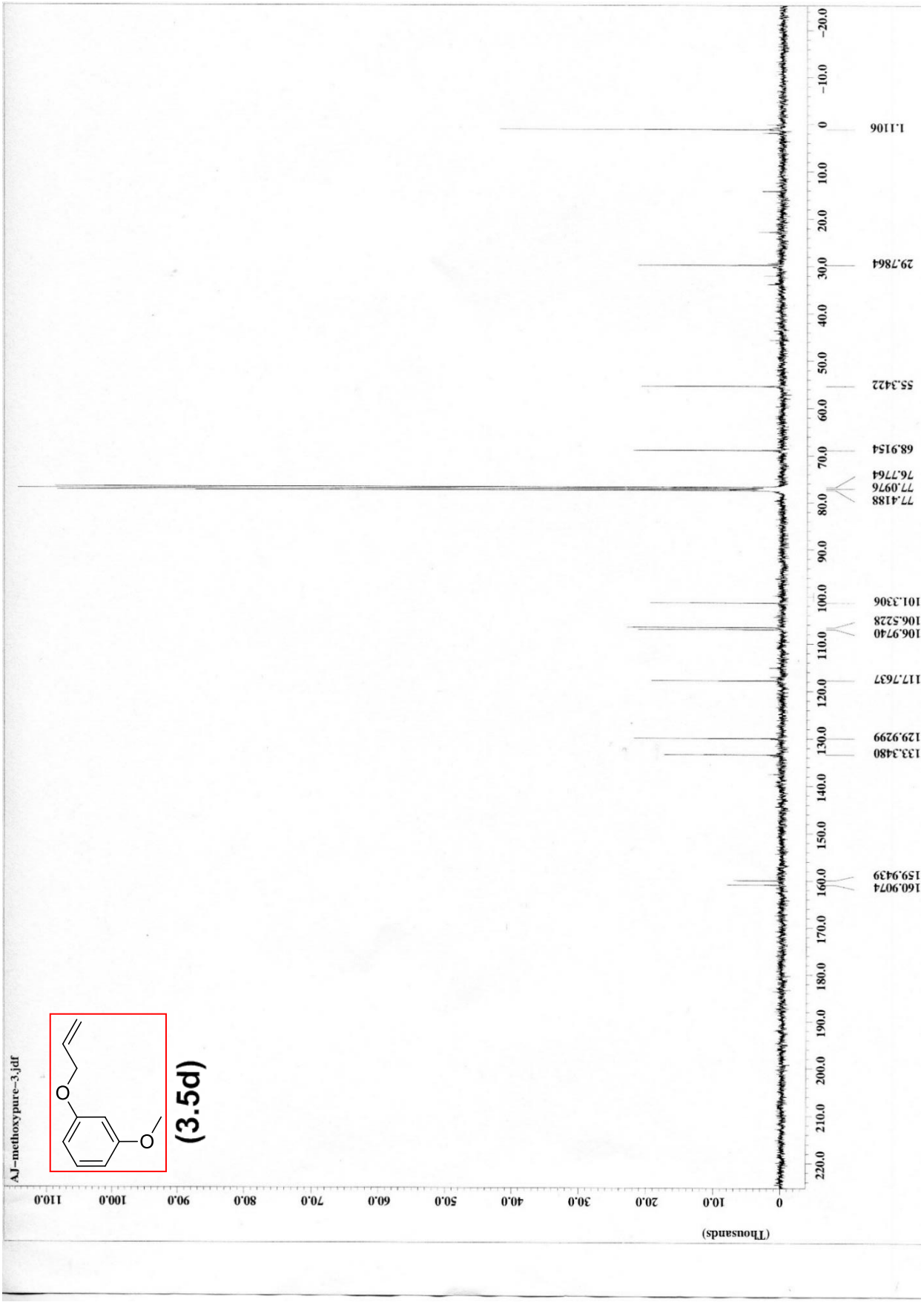
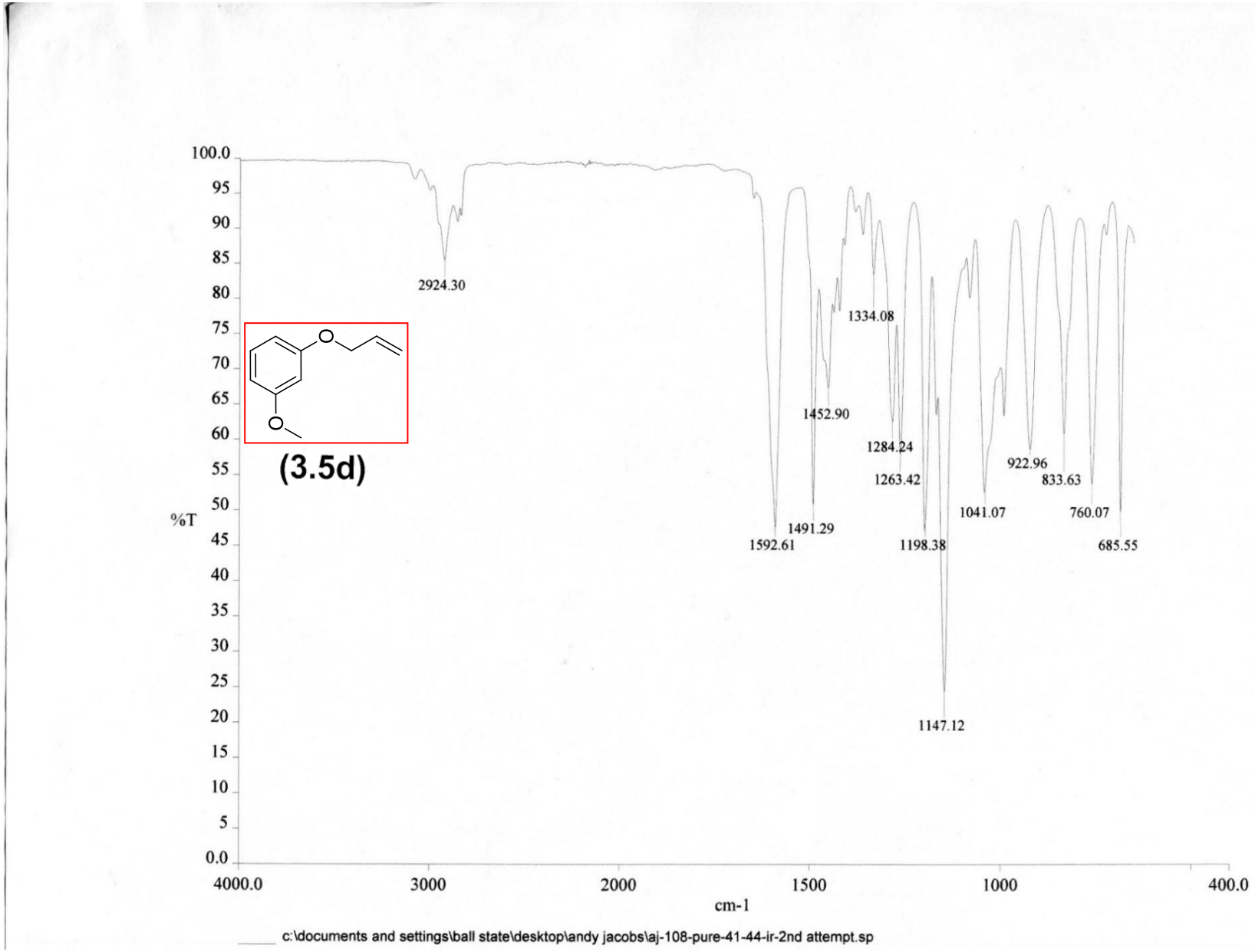
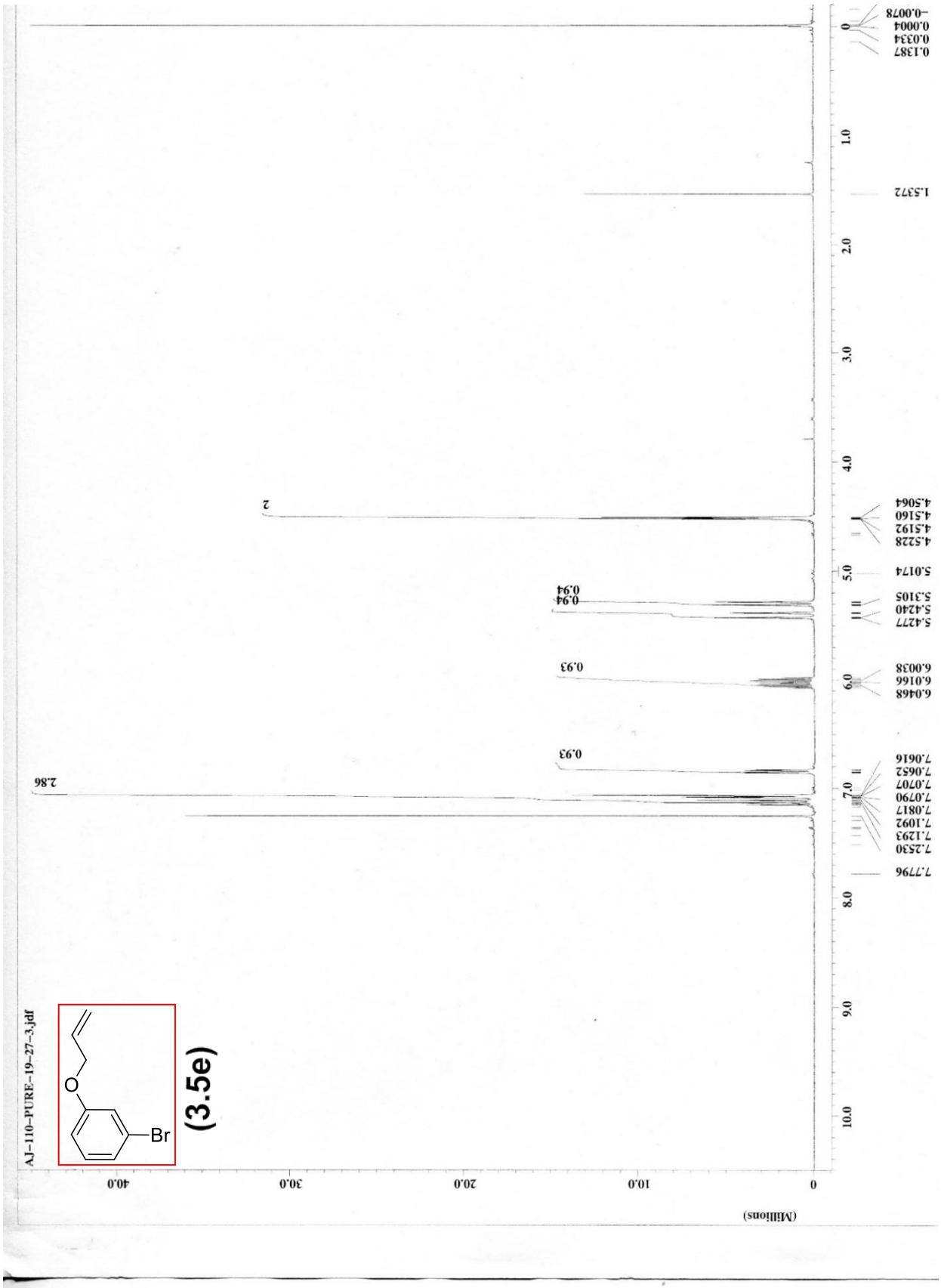
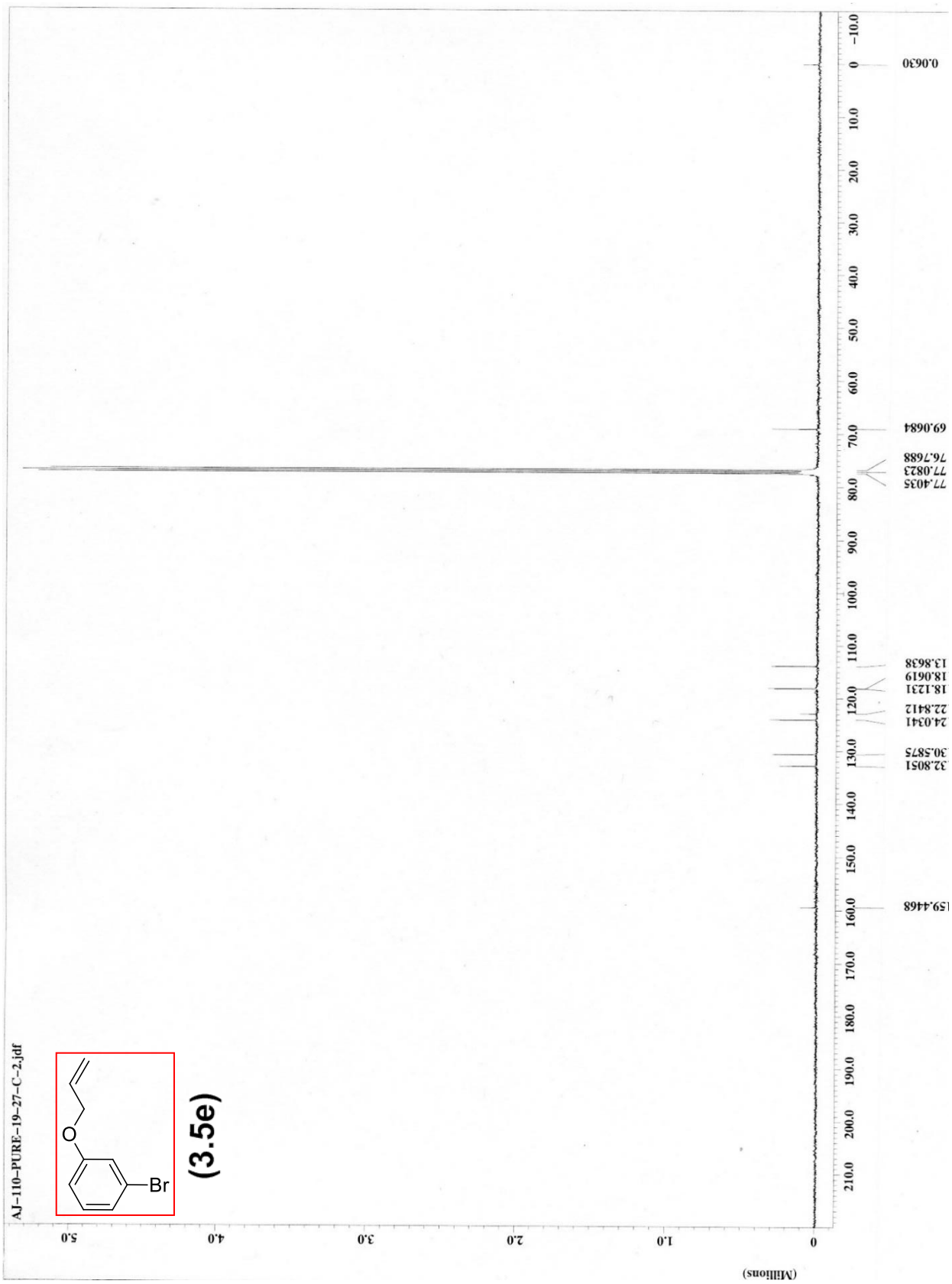
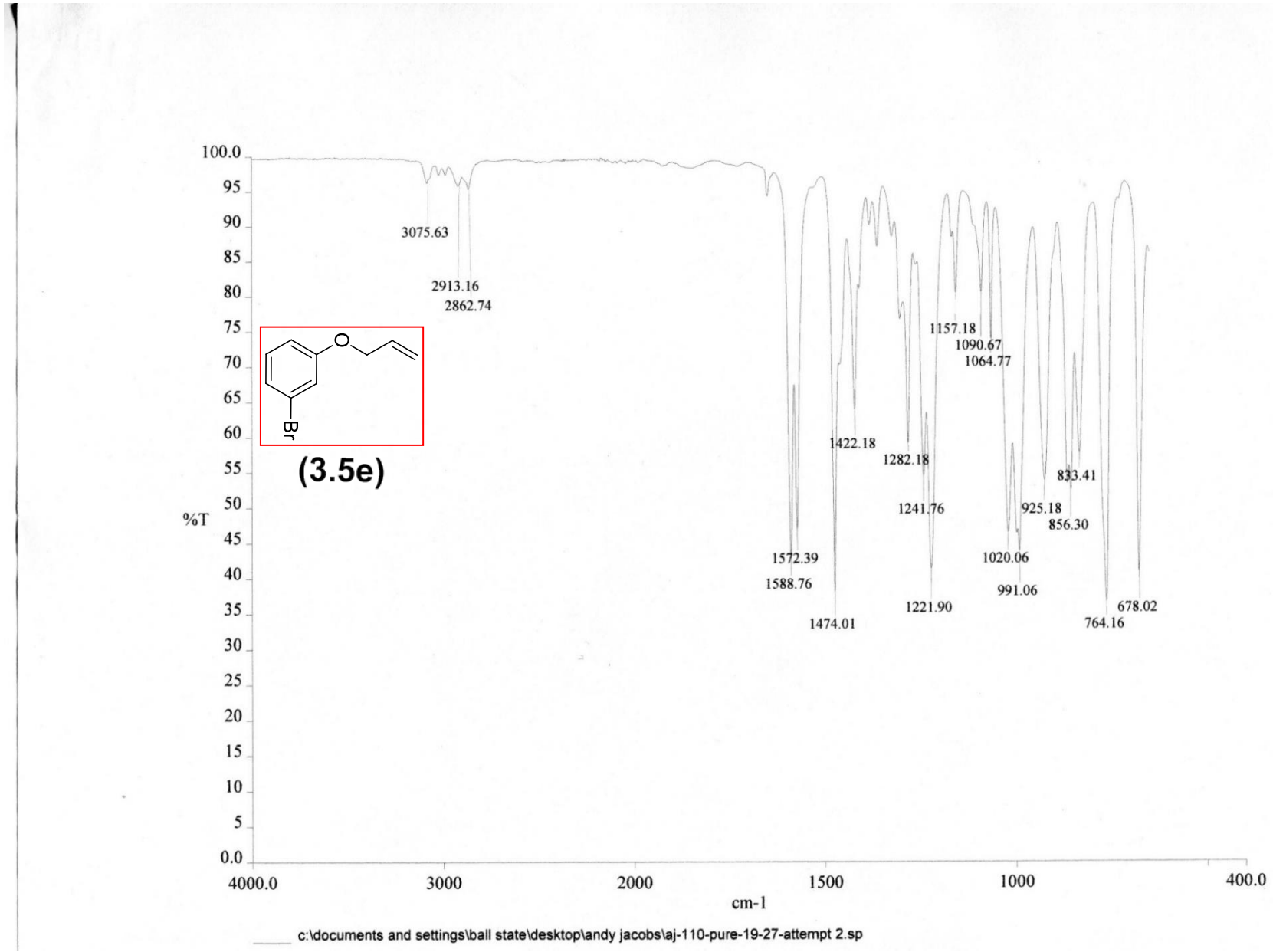
2
0.99
0.98
0.99
3.0
1.02

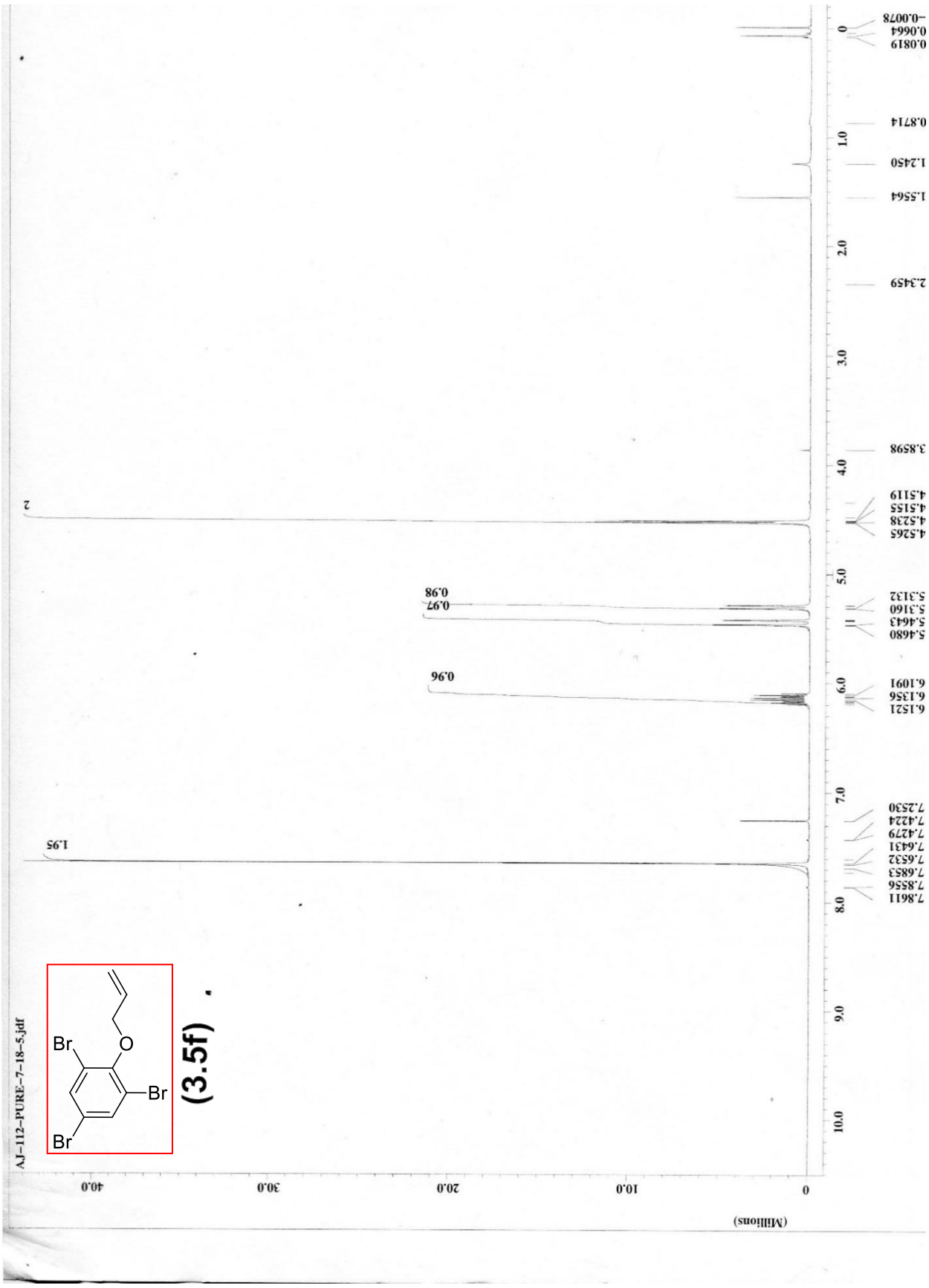

AJ-methoxypure-3.jdf
(3.5d)
(Thousands)
1.1106
29.7864
55.3422
68.9154
76.7764
77.0976
77.4188
101.3306
106.5228
106.9740
117.7637
129.9299
133.3480
159.9439
160.9074

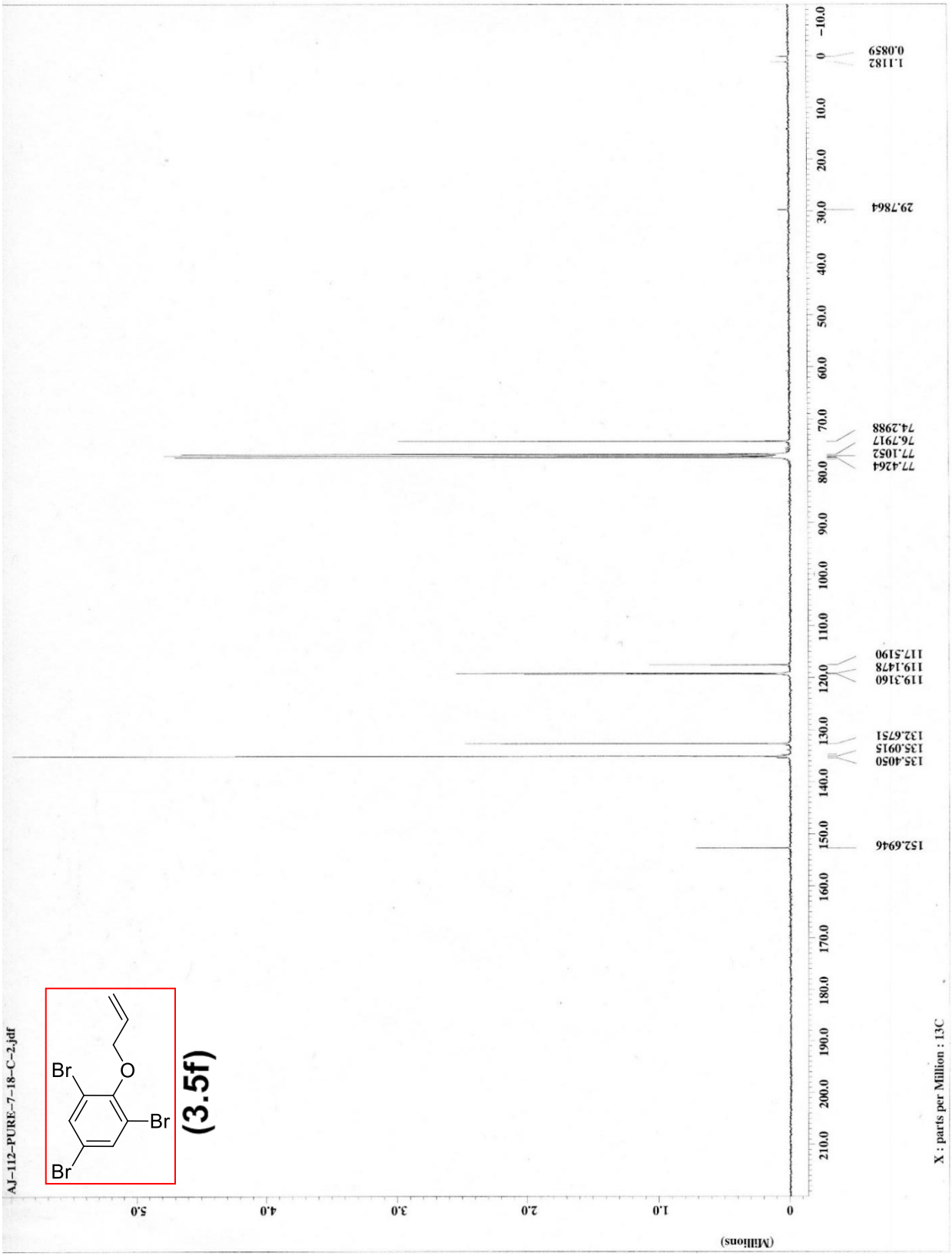

100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
2924.30
1592.61
1491.29
1452.90
1334.08
1284.24
1263.42
1198.38
1147.12
1041.07
922.96
833.63
760.07
685.55
(3.5d)
4000.0
3000
2000
1500
1000
400.0
cm-1
c:\documents and settings\ball state\desktop\andy jacobs\aj-108-pure-41-44-ir-2nd attempt.sp

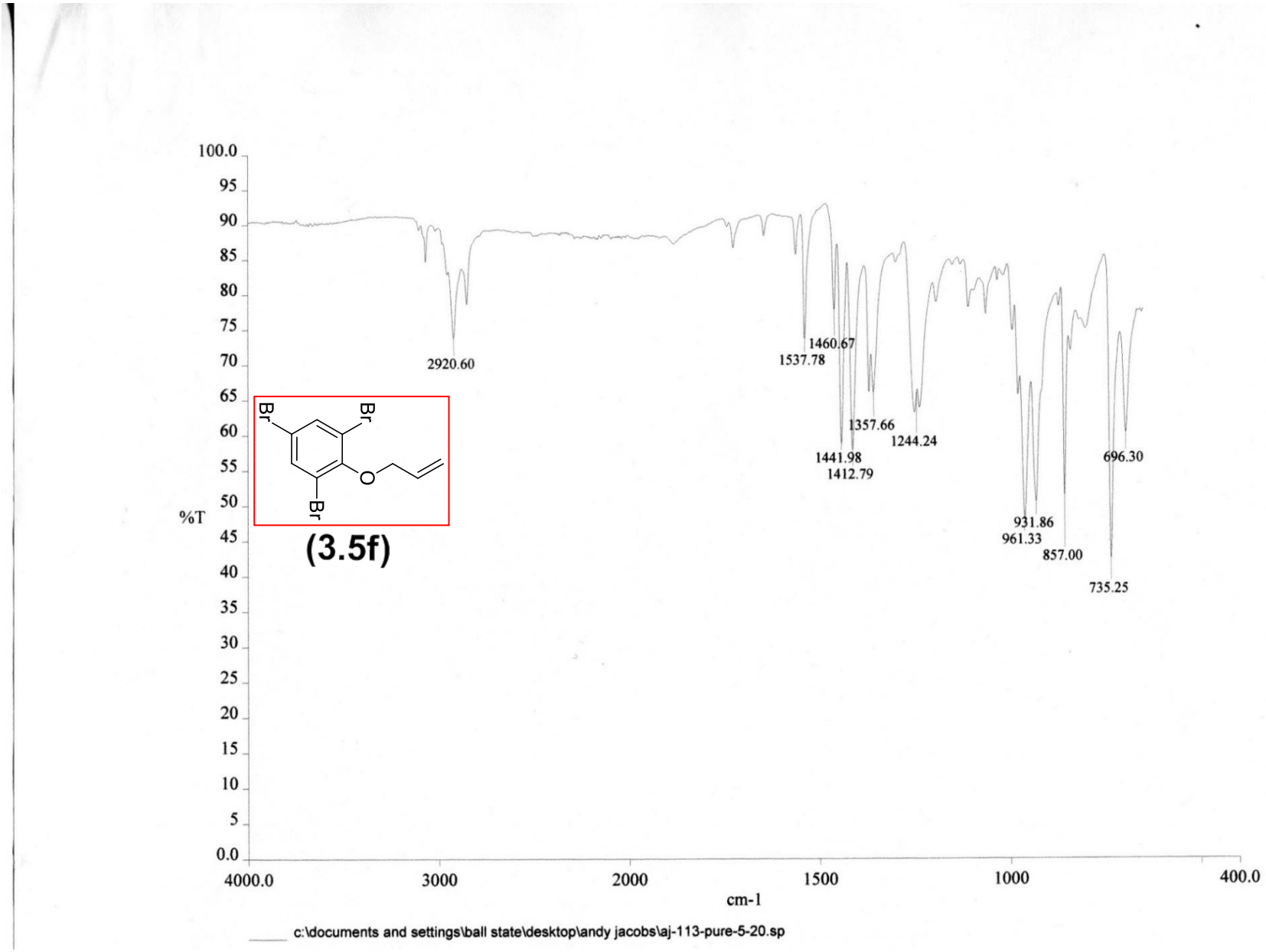

AJ-110-PURE-19-27-3.jdf
(3.5e)
Br
O
(Millions)
0
10.0
20.0
30.0
40.0
2.86
0.93
0.93
0.94
2
1.5372
0.1387
0.0334
0.0004
-0.0078
4.5064
4.5160
4.5192
4.5228
5.0174
5.3105
5.4240
5.4277
6.0038
6.0166
6.0468
7.0616
7.0652
7.0707
7.0790
7.0817
7.1092
7.1293
7.2530
7.7796

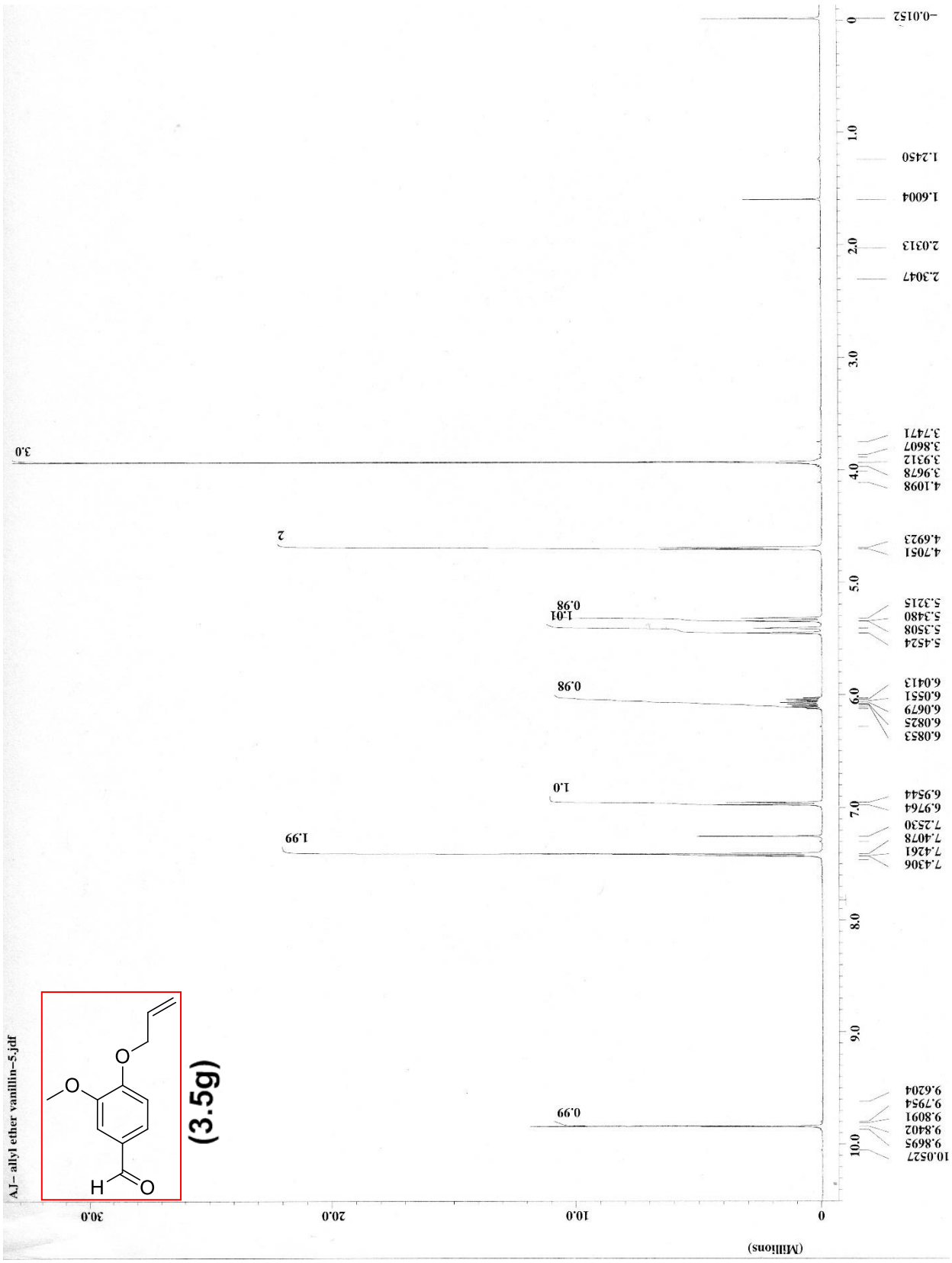

AJ-110-PURE-19-27-C-2.jdf
(3.5e)
O
Br
(Millions)
0.0630
69.0684
77.4035
77.0823
76.7688
32.8051
30.5875
24.0341
22.8412
18.1231
18.0619
13.8638
159.4468

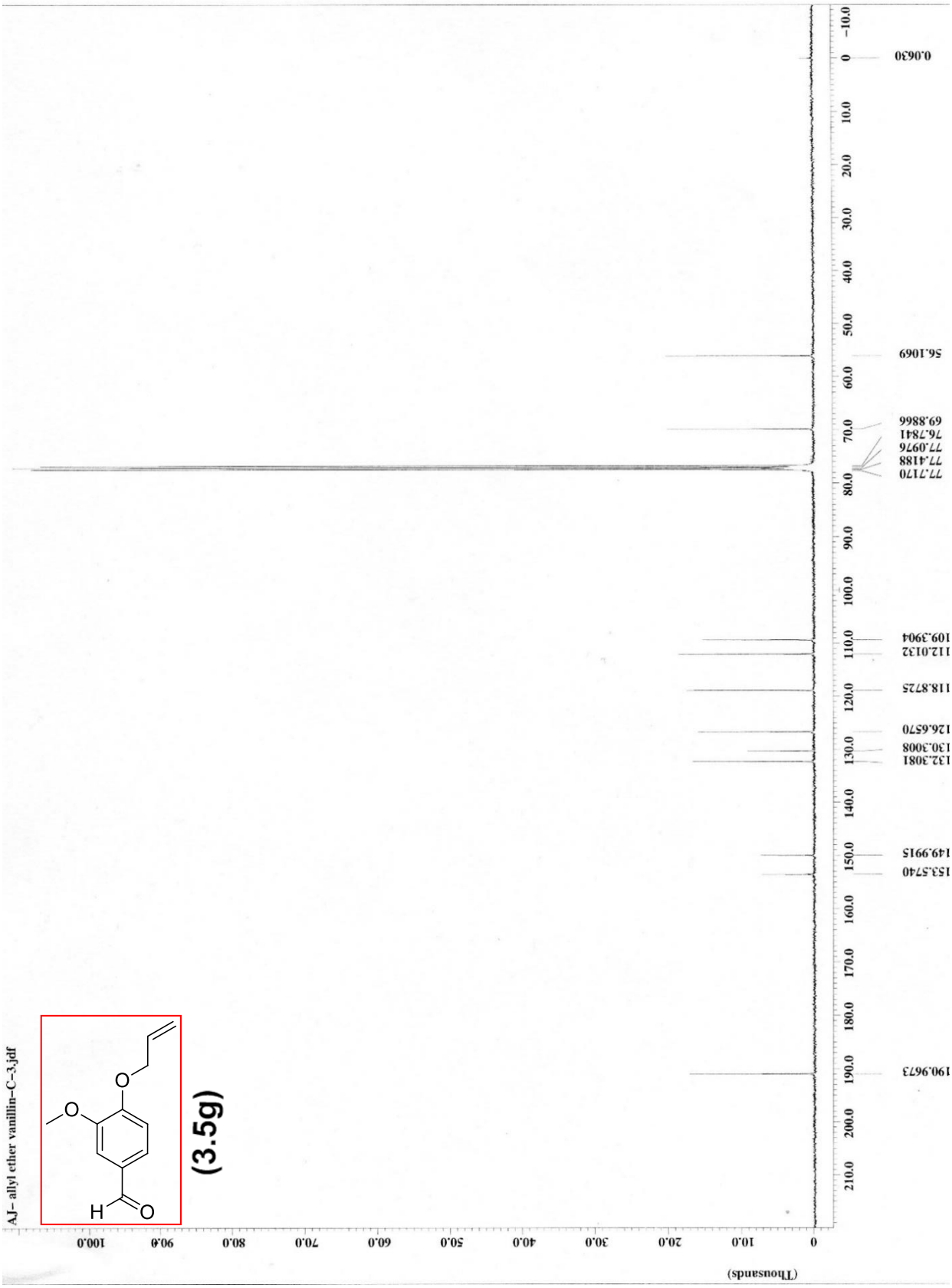

100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
400.0
cm-1
3075.63
2913.16
2862.74
1572.39
1588.76
1474.01
1422.18
1282.18
1241.76
1221.90
1157.18
1090.67
1064.77
1020.06
991.06
925.18
856.30
833.41
764.16
678.02
O
Br
(3.5e)
c:\documents and settings\ball state\desktop\andy jacobs\aj-110-pure-19-27-attempt 2.sp

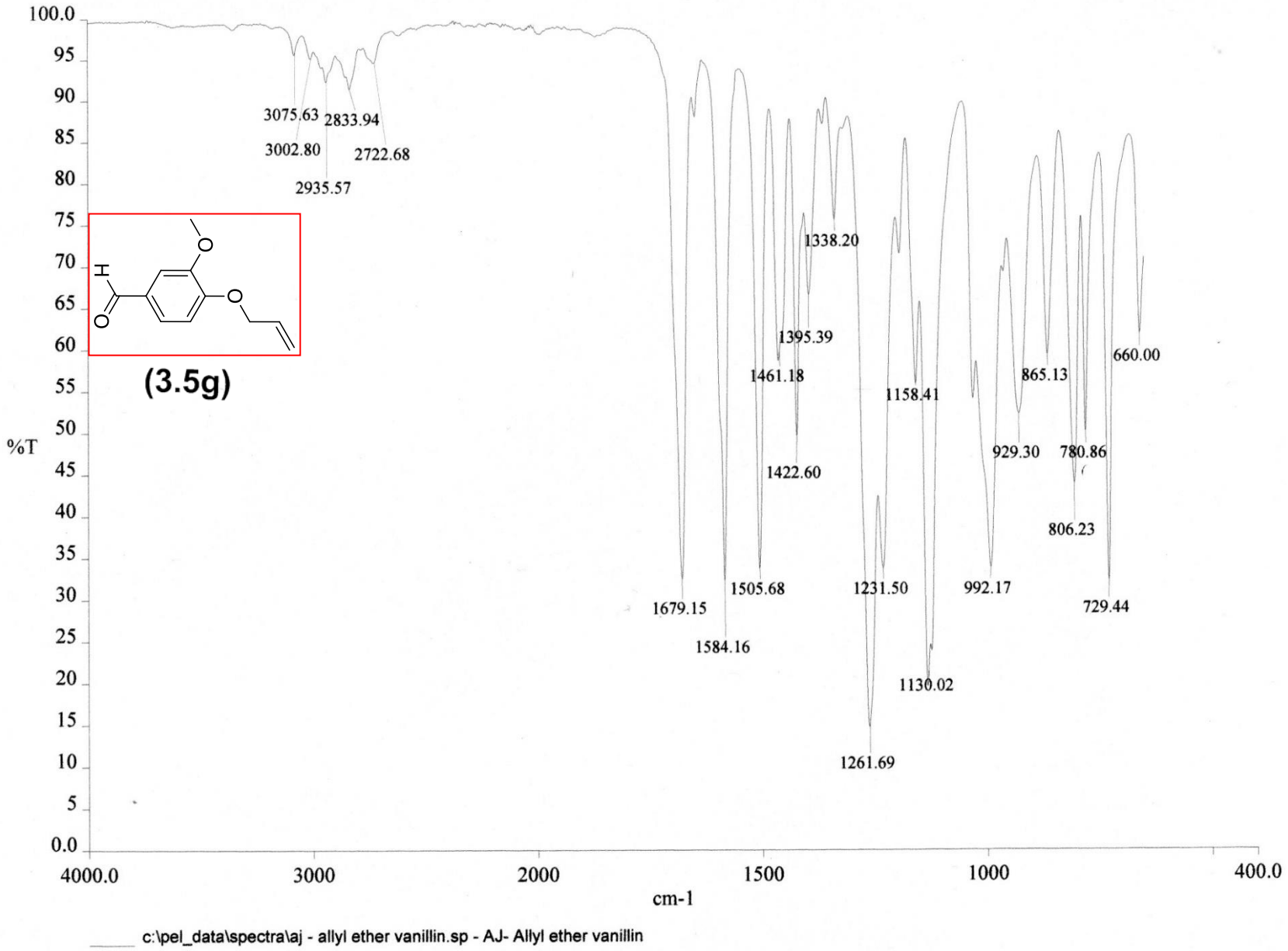

AJ-112-PURE-7-18-5.jdf
Br
O
Br
Br
(3.5f)
(Millions)
0
10.0
20.0
30.0
40.0
1.95
2
0.96
0.97
0.98
7.8611
7.8556
7.6853
7.6532
7.6431
7.4279
7.4224
7.2530
6.1521
6.1356
6.1091
5.4680
5.4643
5.3160
5.3132
4.5265
4.5238
4.5155
4.5119
3.8598
2.3459
1.5564
1.2450
0.8714
0.0819
0.0664
-0.0078

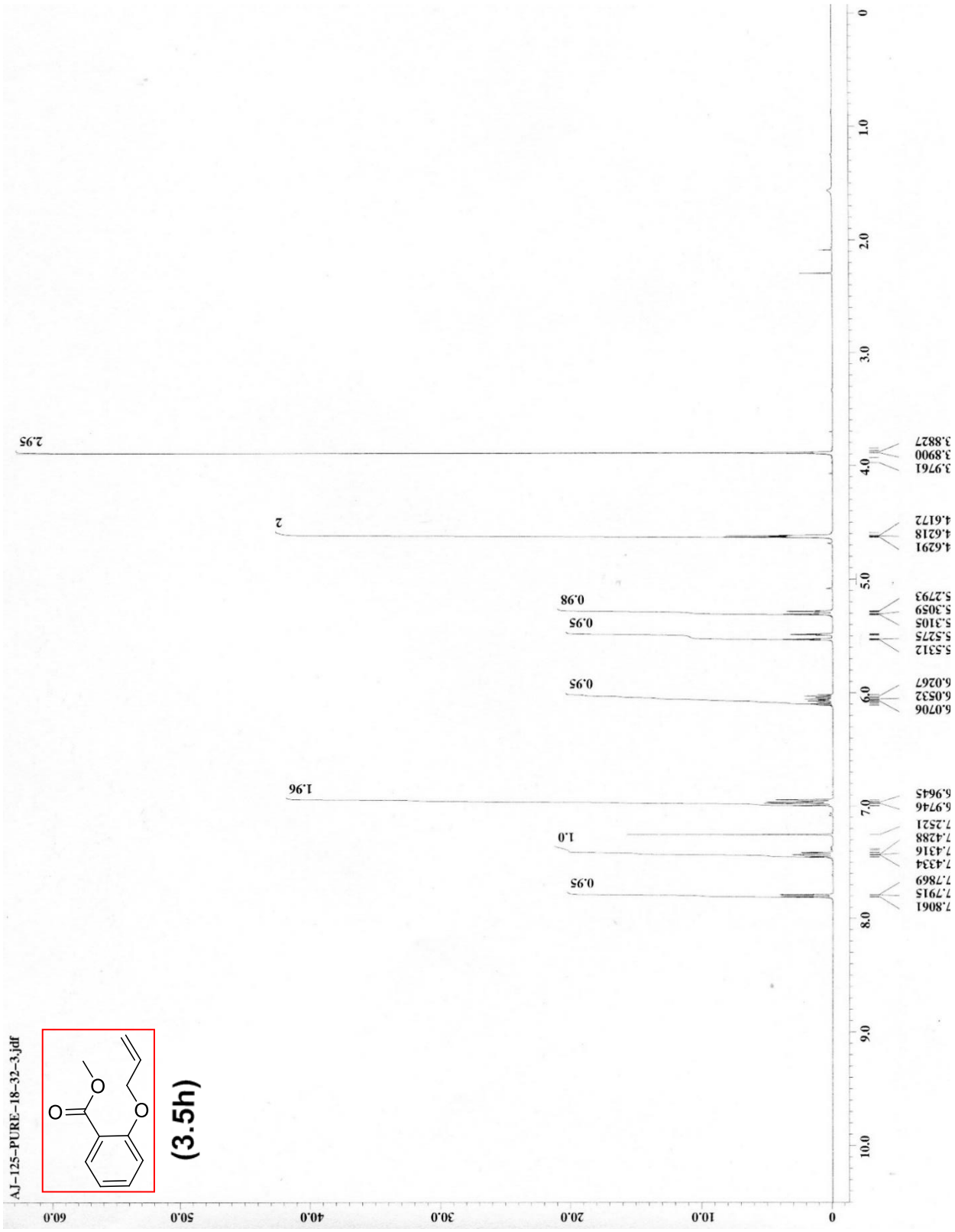

AJ-112-PURE-7-18-C-2.jdf
Br
O
Br
Br
(3.5f)
(Millions)
X : parts per Million : 13C
152.6946
135.4050
135.0915
132.6751
119.3160
119.1478
117.5190
77.4264
77.1052
76.7917
74.2988
29.7864
1.1182
0.0859

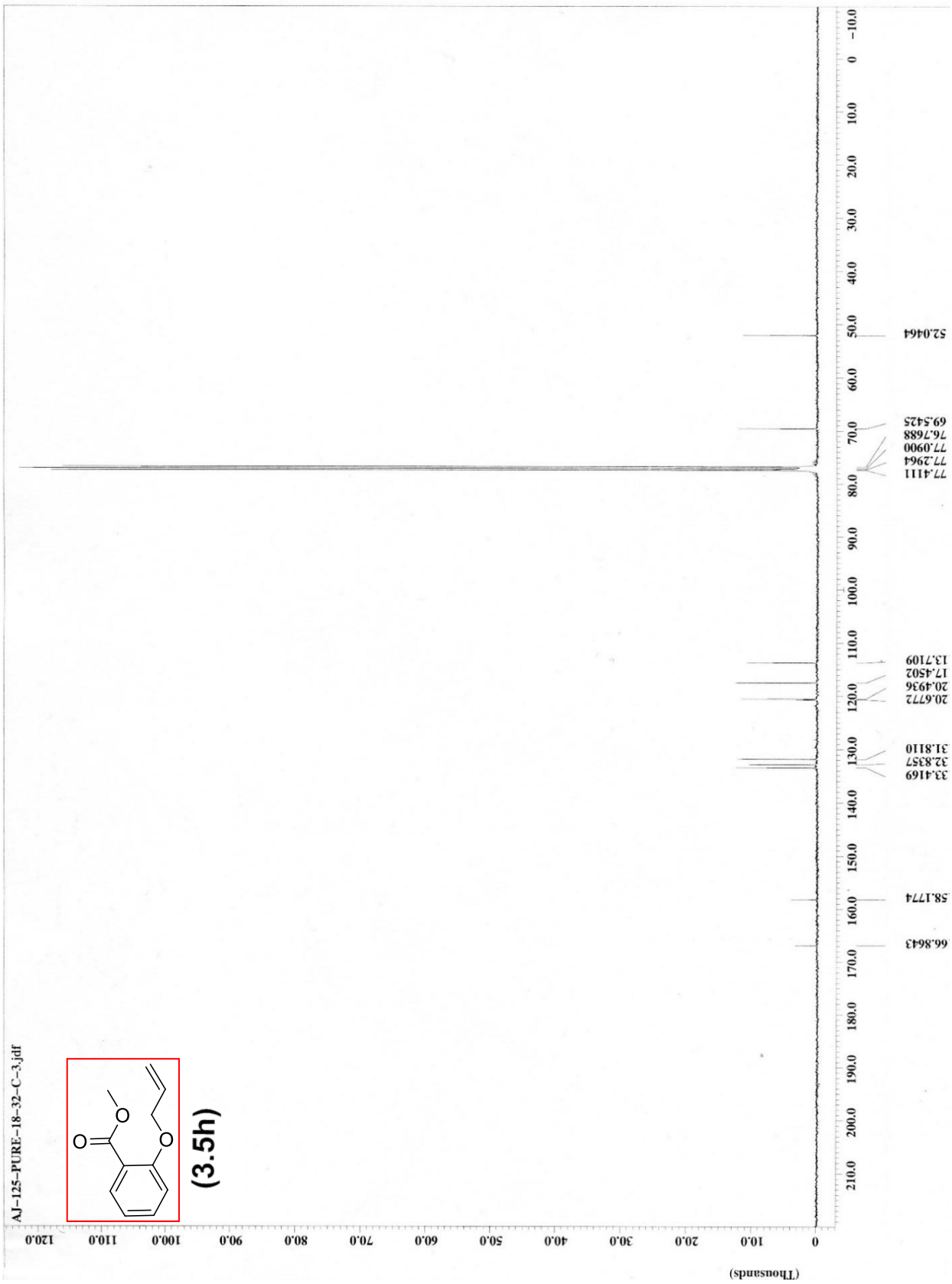

100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
400.0
cm-1
2920.60
1537.78
1460.67
1441.98
1412.79
1357.66
1244.24
961.33
931.86
857.00
735.25
696.30
Br
Br
Br
O
(3.5f)
c:\documents and settings\ball state\desktop\andy jacobs\aj-113-pure-5-20.sp

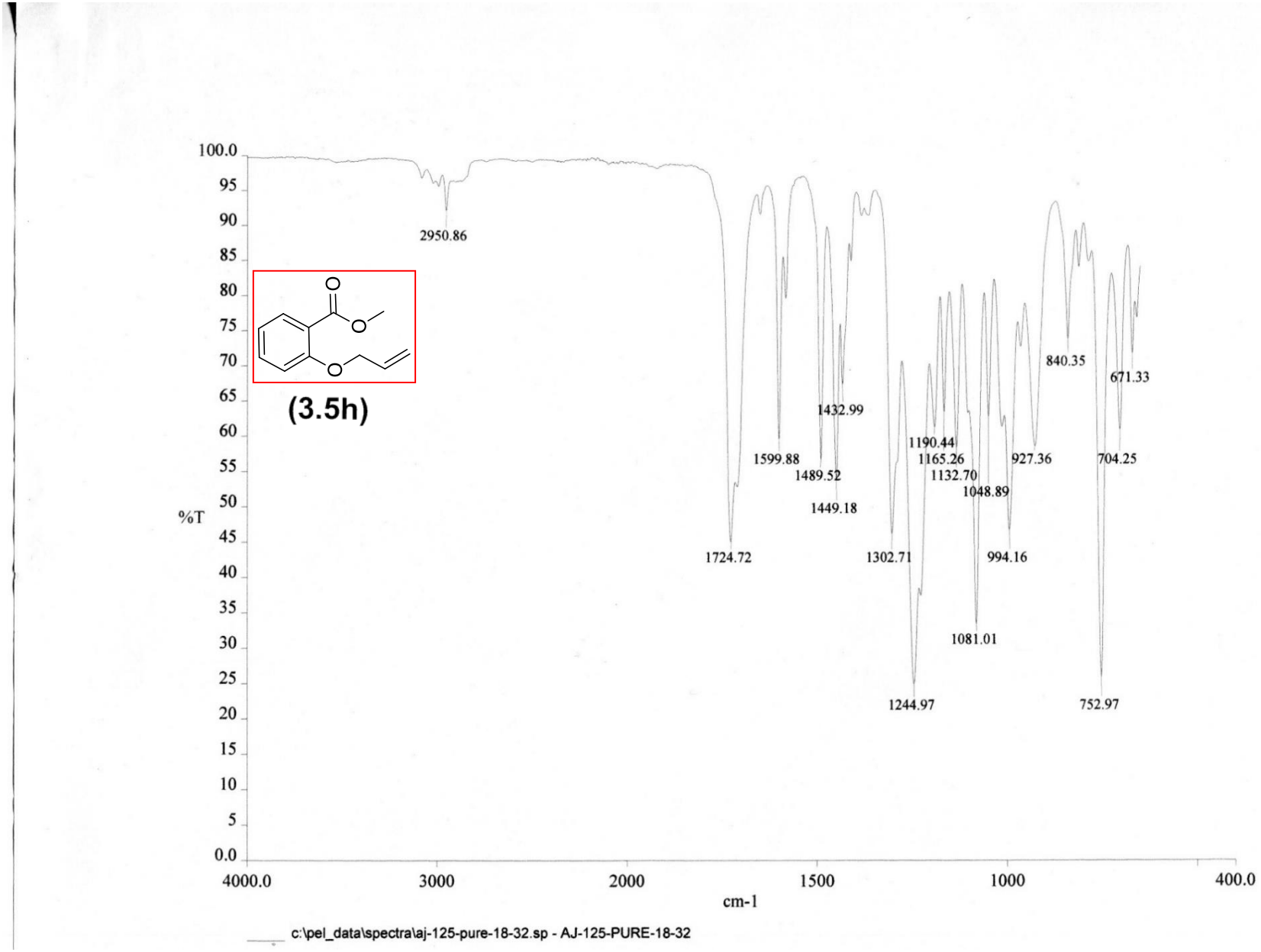

AJ– allyl ether vanillin–5.jdf
(3.5g)
O
O
H
O
(Millions)
30.0
20.0
10.0
0
10.0527
9.8695
9.8402
9.8091
9.7954
9.6204
0.99
7.4306
7.4261
7.4078
7.2530
6.9764
6.9544
1.0
6.0853
6.0825
6.0679
6.0551
6.0413
0.98
1.99
5.4524
5.3508
5.3480
5.3215
1.01
0.98
4.7051
4.6923
2
4.1098
3.9678
3.9312
3.8607
3.7471
3.0
2.3047
2.0313
1.6004
1.2450
-0.0152

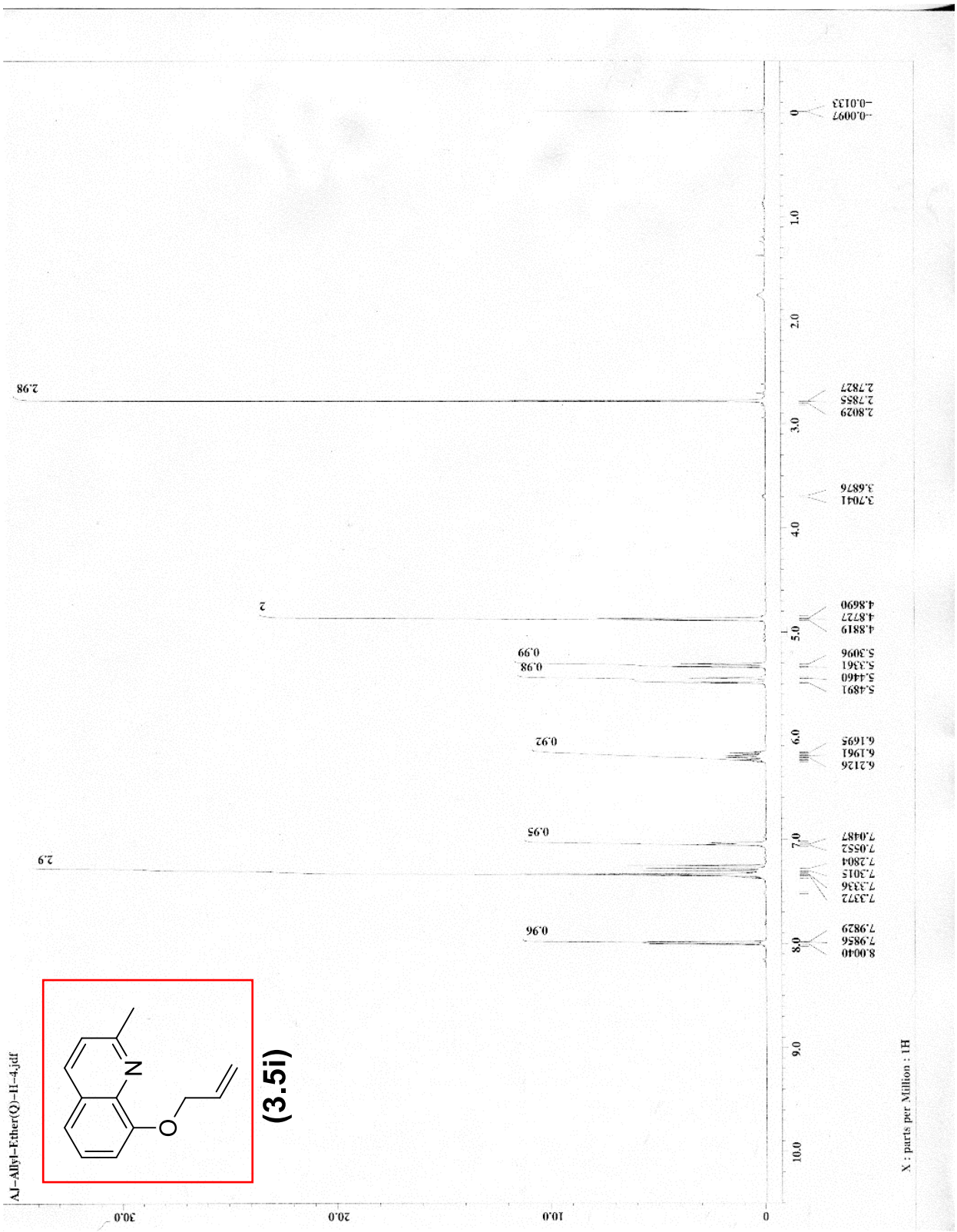

AJ– allyl ether vanillin–C–3.jdf
(3.5g)
O
O
H
O
(Thousands)
0.0630
56.1069
69.8866
76.7841
77.0976
77.4188
77.7170
109.3904
112.0132
118.8725
126.6570
130.3008
132.3081
149.9915
153.5740
190.9673

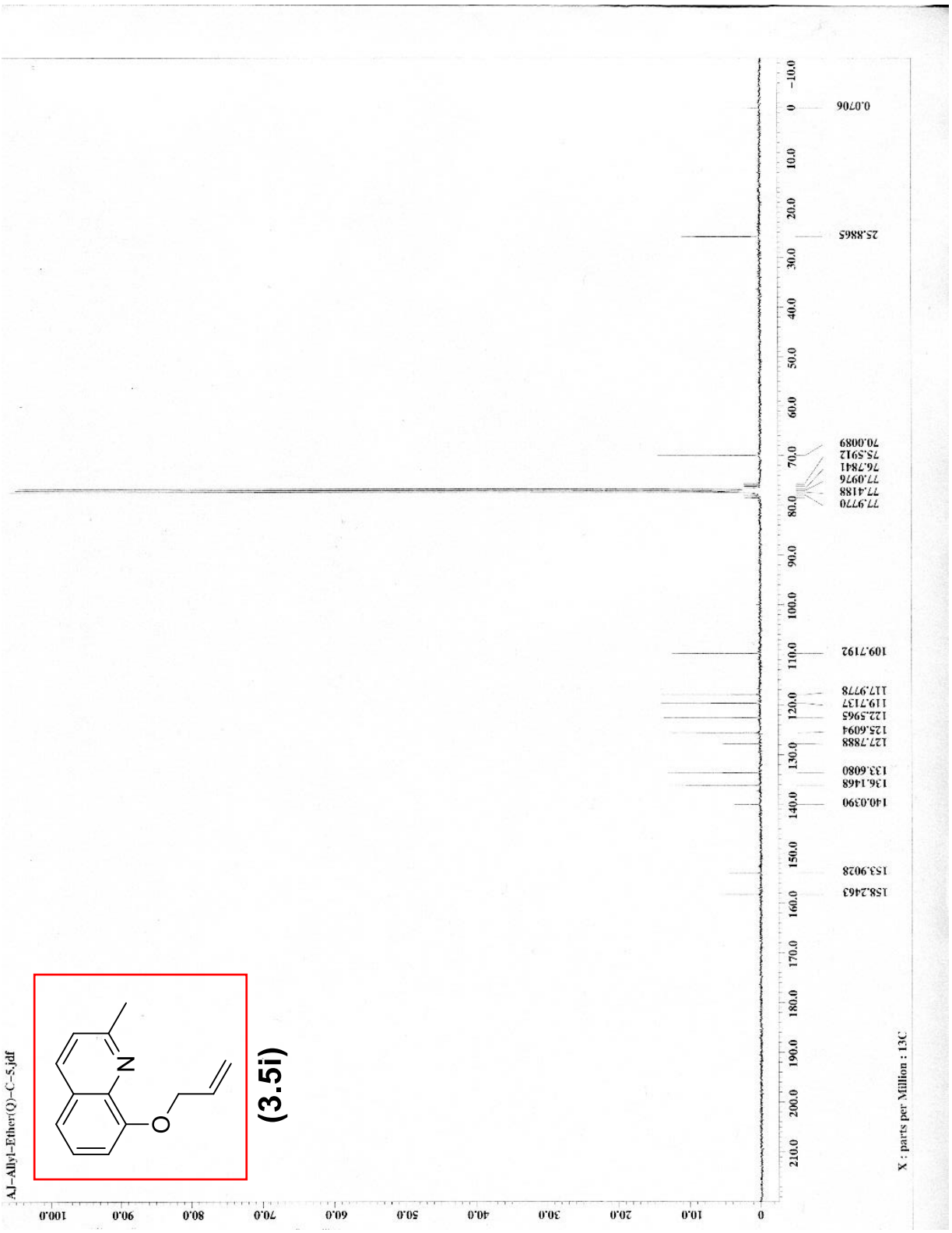

100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
400.0
cm-1
3075.63
3002.80
2935.57
2833.94
2722.68
1679.15
1584.16
1505.68
1461.18
1422.60
1395.39
1338.20
1261.69
1231.50
1158.41
1130.02
992.17
929.30
865.13
806.23
780.86
729.44
660.00
(3.5g)
c:\pel_data\spectra\aj - allyl ether vanillin.sp - AJ- Allyl ether vanillin

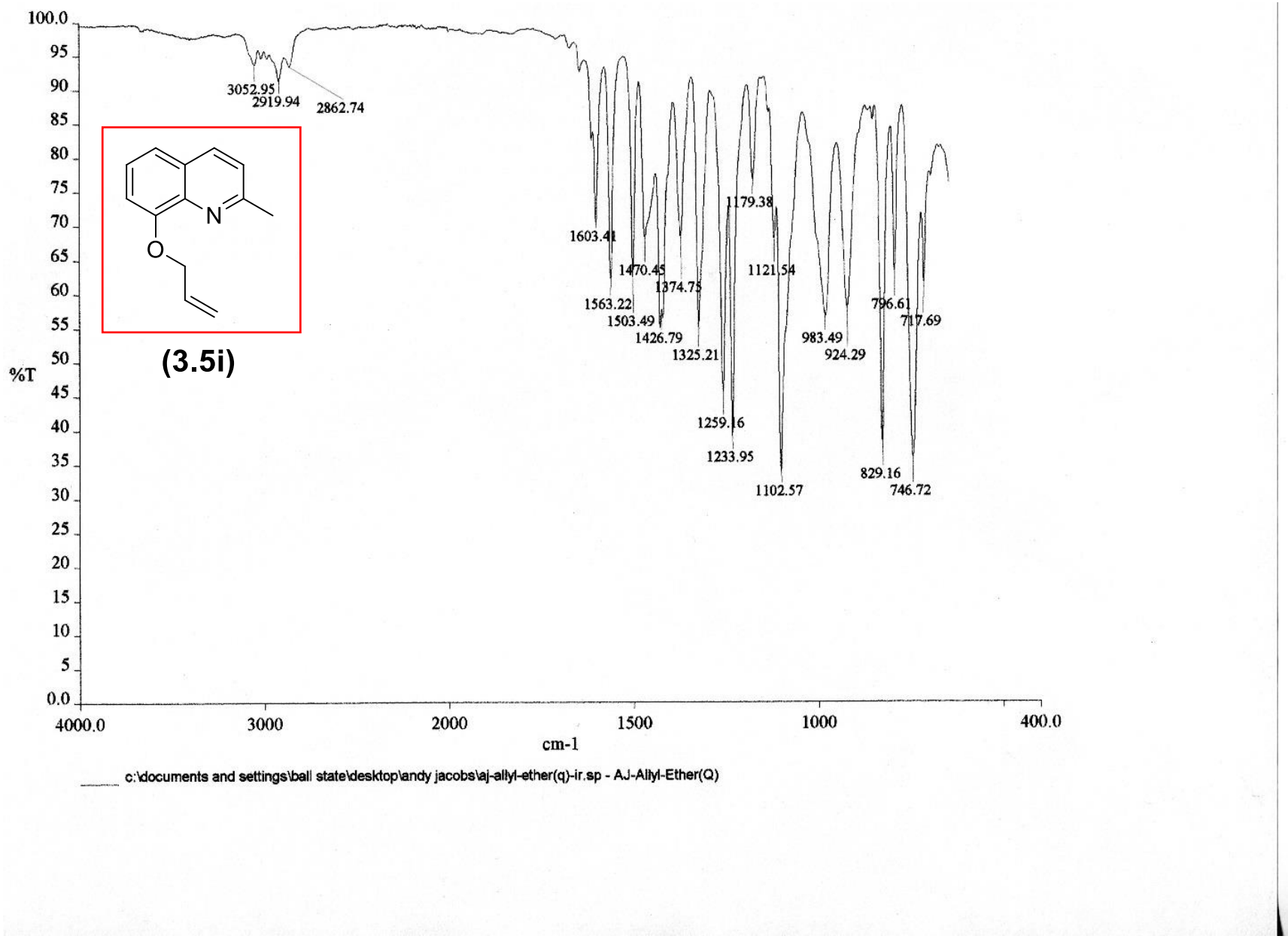

AJ-125-PURE-18-32-3.jdf
(3.5h)
O
O
O
7.8061
7.7915
7.7869
7.4334
7.4316
7.4288
7.2521
6.9746
6.9645
6.0706
6.0532
6.0267
5.5312
5.5275
5.3105
5.3059
5.2793
4.6291
4.6218
4.6172
3.9761
3.8900
3.8827
0.95
1.0
0.95
1.96
0.95
0.95
2
2.95


AJ-125-PURE-18-32-C-3.jdf
(3.5h)
(Thousands)
52.0464
69.5425
76.7688
77.0900
77.2964
77.4111
13.7109
17.4502
20.4936
20.6772
31.8110
32.8357
33.4169
58.1774
66.8643


100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
400.0
cm-1
2950.86
1724.72
1599.88
1489.52
1449.18
1432.99
1302.71
1244.97
1190.44
1165.26
1132.70
1081.01
1048.89
994.16
927.36
840.35
752.97
704.25
671.33
(3.5h)
c:\pel_data\spectra\aj-125-pure-18-32.sp - AJ-125-PURE-18-32


AJ-Allyl-Ether(Q)-H-4.jdf
(3.5i)
X : parts per Million : 1H


AJ-Allyl-Ether(Q)-C-5.jdf
(3.5i)
X : parts per Million : 13C
0.0706
25.8865
70.0089
75.5912
76.7841
77.0976
77.4188
77.9770
109.7192
117.9778
119.7137
122.5965
125.6094
127.7888
133.6080
136.1468
140.0390
153.9028
158.2463


100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
400.0
cm-1
3052.95
2919.94
2862.74
1603.41
1563.22
1503.49
1470.45
1426.79
1374.75
1325.21
1259.16
1233.95
1179.38
1121.54
1102.57
983.49
924.29
829.16
796.61
746.72
717.69
N
O
(3.5i)
c:\documents and settings\ball state\desktop\andy jacobs\aj-allyl-ether(q)-ir.sp - AJ-Allyl-Ether(Q)